SOME EXAMPLES OF BENZOTRIAZOLE-MEDIATED SYNTHESIS

BY

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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Dedicated to all the scientists,

who made this world better

by the power of understanding.

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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By

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Chairman: Alan R. Katritzky, FRS
Major Department: Chemistry

(*N*,*N*-Dialkylaminoalkyl)benzotriazoles were used as a generalized iminium ion equivalent in the previously reported thiazolium salt catalyzed synthesis of α-amino ketones from aldehydes. This method enabled the synthesis of some α-substituted α-amino ketones which were beyond the literature method. The elaborated "no-base-added" conditions greatly enhanced the selective proceeding of the desired reaction against benzoin and Mannich reactions which are inherent side-reactions with the method.

N,*N*-Dimethylbenzotriazolylmethyleneiminium chloride has been prepared by two methods in high yields. It resembles Vilsmeier reagent in reacting with nucleophiles. It was found that it could be deprotonated to generate dimethylaminobenzotriazolyl carbene, which was trapped with phenyl isocyanate in a [1+2+2] cycloaddition to obtain hydantoins with various functionalities at the 5-position and with *trans*-dibenzoylethylene in a [1+4] cycloaddition to give substituted furans.

BetMIC (benzotriazol-1-yl-methyl isocyanide) was used in comparison with TosMIC (*p*-tolylsulfonylmethyl isocyanide) in synthesizing pyrroles and imidazoles. In

many cases where TosMIC gave poor results, BetMIC gave better yields, especially in reacting with less reactive electrophiles.

Diastereoselective *trans*-olefinations of carboxylic esters has been accomplished by reacting benzylic or allylic benzotriazole derivatives with carboxylic esters to prepare α-(benzotriazol-1-yl) ketones, subsequent reduction of the α-(benzotriazol-1-yl) ketones, and finally low-valent titanium-effected dehydroxybenzotriazolylation. Elaboration of this method onto *N*-protected α-amino acid esters gave allylamines with virtually full retention of chirality. Mechanistic aspects of the dehydroxybenzotriazolylation are discussed. The difficulty for the β-hydroxyamino system to proceed the reductive cleavage under the low valent titanium conditions was circumvented.

CHAPTER 1
GENERAL INTRODUCTION

This work presents some examples of benzotriazole-mediated synthesis in improving known organic transformations or achieving new organic transformations.

The 1-benzotriazolyl group (Bt) (Figure 1.1) has the following basic chemical properties:

i). it can activate the α-hydrogen atom to be deprotonated to form the carbanion **1.2** (Figure 1.2), because of the inductive-effect of the electron deficient ring constructed by the three electro-negative nitrogen atoms;

ii). it can activate some α-heteroatoms (for example, halogens) to leave and stabilize the resulting carbocation (Figure 1.3), because of the lone pair of electrons on the nitrogen atom at the 1-position;

iii). it is a good leaving group when it is activated by electron donating effect (*e.g.* from α-heteroatoms, heterocycles, aryl groups, alkenyl groups, etc) (Figure 1.4).

In addition to these properties, benzotriazole is a stable, cheap, and easily recyclable compound. All these features make the Bt group potentially a versatile synthetic auxiliary. Over the past years, Katritzky and his co-workers have intensively investigated the use of benzotriazole as a synthetic auxiliary in a wide variety of organic transformations [91T2683] [94S445] [94MI31]. The work of this thesis is an effort to further explore benzotriazole-mediated synthetic utility. Chapter 2, Chapter 3 and Chapter 4 involve applying the established benzotriazole chemistry to some known synthetic transformations

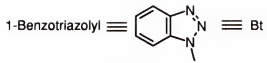


Figure 1.1

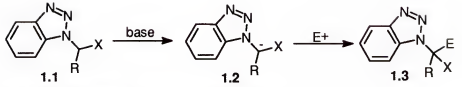


Figure 1.2

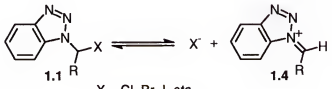


Figure 1.3

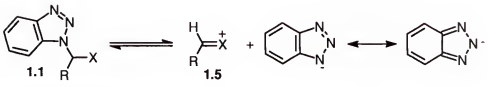


Figure 1.4

to improve these transformations. Chapter 5 reports the work of elaborating a new transformation by applying a recently discovered transformation to different functional groups.

The leaving ability of benzotriazolyl group is most fundamental in the benzotriazole-mediated synthesis. Unlike halogens, the benzotriazolyl group is not a very

good leaving group when attached to simple alkyl groups. However, when in conjunction with nitrogen atoms at the α-carbon, an equilibrium exists as shown in Figure 1.4 (X = NR^1R^2) [91T2683]. Compared with halogen analogues, the Bt adduct **1.1** is more stable, easily prepared and versatile [91T2683]. The Bt adducts **1.1** have been successfully used in Mannich type reactions as a generalized iminium ion **1.5** equivalent (X = NR^1R^2) [91T2683]. Work in Chapter 2 was an effort to apply this general iminium ion equivalent to a reported method [88S314] of synthesizing α-amino ketones **1.8** from aldehydes **1.6** (Figure 1.5). This work utilized the Mannich reaction to generate the iminium ion equivalent and the benzoin condensation to manipulate the aldehyde carbonyl group into the acyl anion equivalent. The elaboration of the "no-base-added" condition not only greatly enhanced the selective proceeding of the desired reaction against the Mannich reaction and the benzoin reaction but also provided an improvement to the original literature method [88S314].

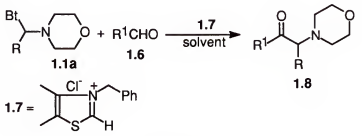
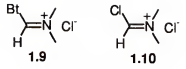


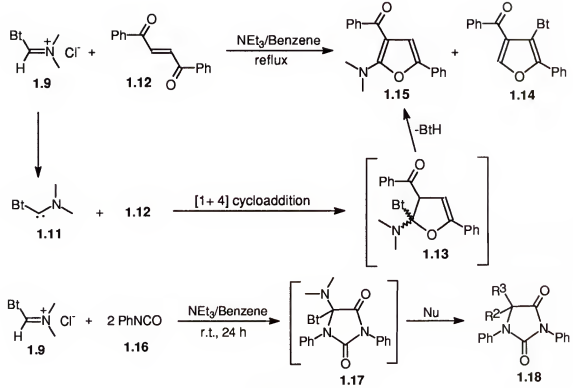
Figure 1.5

The electron-donating property of a Bt group (Figure 1.3) makes it different from some other groups (*e.g.*, cyano and phenylsulfonyl groups) which also possess both anion-stabilizing effect and leaving ability. Chapter 3 describes the study of *N,N*-dimethylbenzotriazolylmethyleneiminium chloride **1.9** as a more stable substitute for the Vilsmeier reagent **1.10**. The electron donating effect of the Bt group should make **1.9** more



1.9 **1.10**

Figure 1.6



1.9 **1.12** **1.15** **1.14**

1.11 **1.13**

1.9 **1.16** **1.17** **1.18**

Figure 1.7

stable than **1.10** (Figure 1.6). The interesting finding of the formation of dimethylamino-benzotriazolyl carbene **1.11** along the way led to its trapping in a novel [1+4] cycloaddition with *trans*-dibenzoylethylene **1.12** to give furans **1.14** and **1.15**, and in a [1+2+2] cycloaddition with phenyl isocyanate **1.16** in reactions which demonstrated some synthetic utility in approaching the hydantoin **1.18** system (Figure 1.7).

Of the benzotriazole-mediated organic transformations achieved by Katritzky and his co-workers, most utilize the nucleophilic attack from α-carbanions of Bt derivatives to construct carbon-carbon bonds (Figure 1.2), followed by elimination or substitution of Bt

groups to obtain various functionalities [91T2683] [94S445] [94MI31]. As mentioned above, Bt groups stabilize α-carbanions only by the inductive effect and they are easier to be eliminated or substituted when they are activated by electron donating effect or driven by special thermodynamic favors (*e.g.*, to obtain aromaticity). Thus, Bt groups are generally used in conjunction at the α-carbon positions with other functional groups such as heteroatoms (O, S, Si), aryl rings, multiple bonds, etc, (Figure 1.2) to stabilize the α-carbanion and/or to activate Bt groups as good leaving groups [91T2683] [94S445] [94MI31]. The weaker anion-stabilizing effect of the Bt group (than that of the tosyl group) was utilized for the higher reactivity of the anion of BetMIC (benzotriazol-1-yl-methyl isocyanide) derivatives **1.19** in the syntheses of imidazoles **1.21** and pyrroles **1.23** (Figure 1.8) in comparison with TosMIC (*p*-tolylsulfonylmethyl isocyanide and its derivatives) anion as reported in Chapter 4.

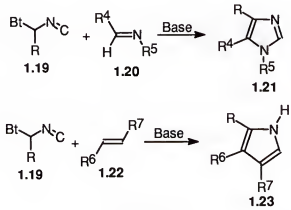
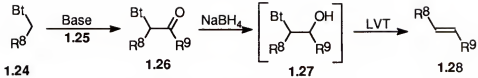


Figure 1.8

Carbon-carbon bond formation *via* nucleophilic attack of carbanions on electrophiles is one of the most well-established method in organic synthesis [90MI55]. The interest of benzotriazole-mediated synthesis *via* nucleophilic attack lies in the way Bt



R8 = aryl or alkenyl; **1.25** = R^9COOR^{10}; R^{10} = Me or Et;
LVT = $TiCl_3/Li$, $TiCl_3/Zn$-Cu

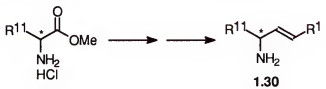


Figure 1.9

groups behave as leaving groups to obtain different functionalities after the carbon-carbon bond formation. Apart from the common substitutions and β-H eliminations, an interesting reductive elimination of β-hydroxy benzotriazoles **1.27** under low valent titanium conditions has recently been reported by Katritzky and Li [97JOC238]. Chapter 5 reports an elaboration of combining the well-established carbon-carbon bond formation via nucleophilic attack of the benzylic/allylic benzotriazole **1.24** anion on carbonyl compounds, reduction, and finally the low valent titanium dehydroxybenzotriazolylation to achieve diastereoselective *trans*-olefination of carboxylic ester groups. Of special interest is the application of this procedure to α-amino acid esters **1.29** to synthesize chiral allylamines **1.30** with retention of asymmetry (Figure 1.9).

CHAPTER 2
A THIAZOLIUM SALT-CATALYZED SYNTHESIS OF α-AMINO KETONES FROM ALDEHYDES AND (*N*,*N*-DIALKYLAMINOALKYL)BENZOTRIAZOLES

2.1 Introduction

Iminium ions can react with carbanions or their equivalents to form carbon-carbon bonds and introduce nitrogen atoms. The Mannich reaction embodies such elaborations and have been used widely in organic synthesis [42MI303] [59MI1] [60MI1] [73S703] [96JACS9202]. An interesting example is the synthesis of α-amino ketones **2.4** via a combination of Mannich reaction (generating the iminium ions **2.9** or their equivalents **2.8** *in situ*) and benzoin reaction (manipulating aldehydes **2.2** into acyl anion equivalents **2.7** with the thiazolium salt **2.3**) elaborated by Castells *et al* [88S314] as shown in Figure 2.1. Although the mechanism of the thiazolium salt catalysis is an issue of debate regarding whether the real catalytic species is the thiazolin-2-ylidene or its *cis*/*trans* dimers [58JACS3719] [93TL521] [94H1579] [94TL699] [95T9713] [96TL5019] [96TL8241], the originally proposed mechanism [58JACS3719], as employed in Figure 2.1 with the thiazolin-2-ylidene **2.5** as the catalytic species, still appears most likely. Whatever the mechanism is, the common experimental practice is to add a base to deprotonate the thiazolium salt. Among various methods of synthesizing α-amino ketones [90OPPI399], which are important and versatile compounds in organic synthesis [67CA104826c] [77MI 2251], this method constitutes a unique route starting from aldehydes **2.2**..

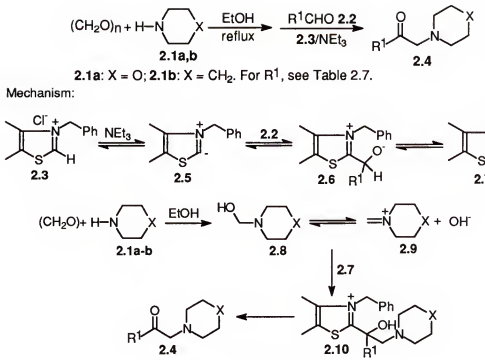
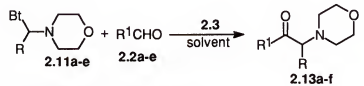


Figure 2.1

Figure 2.2

In general, the classical Mannich reaction has two limitations: i) it is generally limited to formaldehyde in generating iminium ions; ii) it is difficult to prevent multiple reactions. The second limitation has been surmounted by "Eschenmoser Salt" [71AG(E)330]. Because of the ability of the benzotriazolyl adducts **2.11** to ionize (Figure 2.2), they can behave as Eschenmoser Salts, and thus the potential arises to extend the Mannich reaction to general aldehydes. In fact, the *N*-α-(*N*,*N*-dialkylaminoalkyl)benzotriazoles have been used successfully as a generalized iminium ion equivalent in many cases [91T2683].

This chapter reports the use of (N,N-dialkylaminoalkyl)benzotriazoles **2.11a-e** as the generalized iminium ion equivalents to elaborate a more generalized synthesis of the α-amino ketones **2.13a-f** with a substituent R at the α-position (Figure 2.3). The elaboration of a "no-base-added" condition to selectively enhance the desired reaction leading to α-amino ketones **2.13a-f** against the competing Mannich reaction and benzoin reaction is also described.



For designation of each compound, see Table 2.7 and Figure 2.9.

Figure 2.3

2.2 Results and Discussions

Reaction Conditions and Side-reactions

The reaction was first attempted with the same aliphatic aldehyde (isobutyraldehyde, **2.2a**), under the same conditions as described by Castells *et al* [88S314]: 2 eq. of the aldehyde **2.2a**, 0.1 eq. of the thiazolium salt **2.3** and triethylamine (to deprotonate salt **2.3**), ethanol as solvent, except that the benzotriazolyl adduct **2.11a** was used as the reactant (Figure 2.4).

Under such conditions in Figure 2.4, the product obtained, according to ^{1}H NMR, was the same as reported in the literature [88S314]. However, spectral analysis suggested

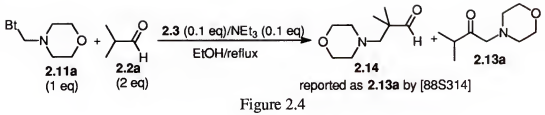


Figure 2.4

that it was actually not the α-amino ketone **2.13a** (actually not detected in the reaction mixture) but the Mannich product, β-amino aldehyde **2.14**. Evidence for this conclusion is as follows: i). two methyl groups appear as a singlet at 1.07 ppm; ii) upon treatment with D_2O, all peaks remained unchanged (eliminating the possibility of an enolate form); iii) the same product **2.14** was obtained with about the same yield by repeating the literature [88S314] method without addition of the catalyst **2.3**, which was needed for the desired reaction; iv) compound **2.13a** was obtained later by changing the reaction conditions (see below in the same section) with the expected ^{1}H-NMR spectrum. In this case of the aldehyde **2.2a** with an enolizable α-H, the undesired Mannich reaction predominated.

Under same conditions (2 eq. of the aldehyde **2.2b**, 0.1 eq. of the thiazolium salt **2.3** and triethylamine, ethanol as solvent), the reaction of benzaldehyde **2.2b** with the benzotriazolyl adduct **2.11a** gave the α-amino ketone **2.13b** in low yield (25%) (Figure 2.5). GC-MS analysis of the reaction mixture provided evidence that benzoin condensation competed with the desired reaction (Table 2.1).

In order to enhance the selective proceeding of the desired reaction against benzoin reaction, a modification of the reaction condition was proposed by considering the reaction scheme shown in Figure 2.6. The product distribution depends on the relative rate of the reaction between the carbanion intermediate **2.7a** and the Bt adduct (desired reaction) **2.11a** to the reaction between the carbanion intermediate **2.7a** with the aldehyde **2.2b** (benzoin reaction). If no triethylamine is added, the benzotriazolyl anion, formed in equilibrium with

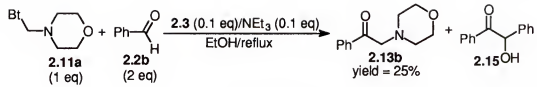


Figure 2.5

Table 2.1. GC-MS Area Percentage of the Reaction Mixture in Figure 2.5.

reaction time	2.0 h	5.0 h	7.5 h	9.0 h
α-amino ketone **13b**	15.3	20.6	21.3	21.9
benzoin **15**	26.4	33.2	31.0	31.0

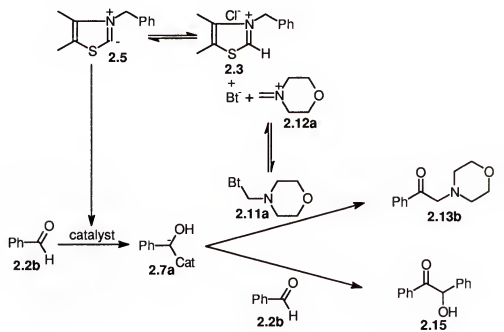


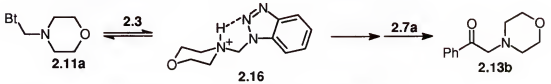
Figure 2.6

the adduct **2.11a**, would function as the base to deprotonate the thiazolium salt **2.3** to give the catalytic species **2.5**; thus, stoichiometrically every carbanion intermediate **2.7a** generated would correspond to one or more free iminium ions **2.12a** which are more reactive than the ion-pairs and the undissociated adduct **2.11a**. This should increase the desired reaction rate relative to that of the undesired benzoin reaction.

This idea turned out to work dramatically well. The same reaction in Figure 2.5 was repeated without adding triethylamine. The yield of the desired product **2.13b** was raised to 58%. GC-MS analysis (Table 2.2) suggests that the benzoin reaction was totally inhibited until the desired reaction was virtually complete (first equivalent of the aldehyde **2.2b** was totally consumed by the desired reaction before the second equivalent started to undergo the benzoin reaction).

Table 2.2. GC-MS Area Percentage of the Reaction Mixture in Figure 2.5 without Adding Triethylamine

reaction time	2.0 h	5.0 h	7.5 h	9.0 h
α-amino ketone **13b**	12.9	19.1	23.8	23.9
benzoin **15**	0.0	0.0	0.0	2.7



See Figures 2.1 and 2.6 for the structure and function of **2.7a**.

Figure 2.7

Apart from the consideration shown in Figure 2.6, another explanation for this result is that the morpholine nitrogen atom of the 1-benzotriazolyl adduct **2.11a** acts as the base to deprotonate thiazolium salt **2.3** (Figure 2.7).

Such "no-base-added" conditions gave the α-substituted α-amino ketone **2.13c** in 44% yield (Figure 2.8). Again, Tables 2.3 and 2.4 show that the product selectivity was enhanced without adding triethylamine.

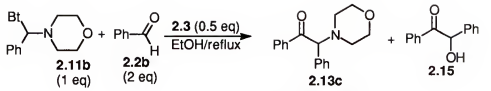


Figure 2.8

Table 2.3. GC-MS Area Percentage of the Reaction Mixture in Figure 2.8

reaction time	2.2 h	5.5 h	8.0 h	19.0 h
α-amino ketone **2.13c**	11.2	15.0	17.6	20.6
benzoin **2.15**	4.3	7.8	9.8	12.3

Table 2.4. GC-MS Area Percentage of the Reaction Mixture in Figure 2.8 in the Presence of 0.1 eq Triethylamine

reaction time	11.0 h	20.0 h
α-amino ketone **2.13c**	9.4	11.4
benzoin **2.15**	10.8	18.7

Such conditions also enhanced the desired reaction against Mannich reaction. Repeating the reaction with isobutyraldehyde **2.2a** (Figure 2.4) without using triethylamine gave a reaction mixture featuring two peaks with molecular ion $M^{+\cdot} = 171$ (**2.14** and **2.13a**) in GC-MS spectrum. ^1H NMR analysis of the reaction mixture suggested that the ratio of compound **2.14** to compound **2.13a** was about 1:2. Apparently, in addition to favoring the generation of free iminium ion as discussed above, "no-base-added" condition disfavored the formation of the enolate and thus enhanced the desired reaction against Mannich reaction. The best result for this case was obtained by running the reaction in acetonitrile with one equivalent of thiazolium salt added. The ratio of **2.14** to **2.13a** was estimated to be

about 1:20 from ^{1}H-NMR analysis of the reaction mixture and the product **2.13a** was isolated in 28% yield.

Extrapolation of the reaction conditions to weakly acidic conditions (by using 0.1 eq of NH_4Cl under the conditions of Figure 2.4) led to only Mannich product **2.14** again. This is probably because the enol form is generated faster and deprotonation of thiazolium salt becomes less favorable under such conditions.

Application of the "No-base-added" Conditions to the Literature Method

Two parallel reactions were attempted using the literature [88S314] method (Figure 2.1) to synthesize **2.13b** (X = O, R^1 = Ph), one in the presence of triethylamine as employed in the literature and the other without adding triethylamine. Table 2.5 and Table 2.6 show the results respectively.

Table 2.5 GC-MS Area Percentage of the Reaction Mixture Using the Literature Conditions in Figure 2.1.

reaction time	2.0 hours	8.0 hours	21.0 hours
α-amino ketone **2.13b**	36.1	53.7	51.1
benzoin **2.15**	34.0	24.7	24.1

Table 2.6 GC-MS Area Percentage of the Reaction Mixture in Figure 2.1 but without Using Triethylamine.

reaction time	2.0 h	8.0 h	21.0 h
α-amino ketone **2.13b**	47.9	55.2	49.3
benzoin **2.15**	0.0	11.7	24.3

By comparing Tables 2.5 and 2.6, it can be seen that after 21 hours of refluxing the parallel two reactions had reached the same status, probably the thermodynamic equilibrium. However, while the reactions were in progress (2 h and 8 h), the selectivity of the "no-base-added" conditions was remarkable. It can be rationalized again that under the "no-base-added" conditions the benzoin reaction started only after the desired reaction was virtually complete (consuming the first equivalent of the aldehyde). In order to confirm the rationale, the reactions were carried out with one equivalent of the aldehyde (R^1 = Ph, **2.2b,** Figure 2.1): the presence of triethylamine gave 32% yield while the "no-base-added" conditions gave 52% yield. This also explains why the literature [88S314] used two equivalents of the aldehydes **2.2** to increase the yields.

Synthesis

Six α-amino ketones **2.13a-f** were synthesized by using the "no-base-added" conditions (Figure 2.3). The results are summarized in Table 2.7.

While the yield has not been optimized, increasing the amount of thiazolium salt up to one equivalent was observed to increase the yield. In attempting to synthesize more α-amino ketones of different R^1 and R groups, it was found that the reaction may undergo cross-over shown in Figure 2.9.

For example, when R^1 = Ph, R = *p*-chlorophenyl, an intractable mixture of all the possible four products **2.13c,e,g,h** was obtained after column chromatography. The mixture featured four peaks of comparable integration at around 5.9 ppm in the ^{1}H NMR spectrum which is characteristic of the CH group between the carbonyl group and the amino group. GC-MS analysis of the same sample featured four GC peaks of comparable percentages with mass spectra characteristic of **2.13c,e,g,h** (see the Experimental). The MS spectra of the α-amino ketones features the base peak shown in Figure 2.10.

Table 2.7. Synthesis of α-Amino Ketones **2.13a-f** According to Figure 2.3.

entry	**2.2**, R^1 (eq)	**2.11**, R (eq)	**2.3** (eq)	time	**2.13**, yield (%)
1	**2.2a**, *i*-Pr (2)	**2.11a**, H (1)	1.0	72 h	**2.13a***, 28
2	**2.2b**, Ph (2)	**2.11a**, H (1)	0.1	8 h	**2.13b**, 58
3	**2.2b**, Ph (2)	**2.11b**, Ph (1)	0.5	24 h	**2.13c**, 44
4	**2.2c**, *p*-NCC_6H_4 (0.5)	**2.11c**, *p*-$MeOC_6H_4$ (1)	0.5	6 h	**2.13d**, 42
5	**2.2d**, *p*-ClC_6H_4 (2)	**2.11d**, *p*-ClC_6H_4 (1)	0.5	36h	**2.13e**, 46
6	**2.2e**, *p*-MeC_6H_4 (2)	**2.11e**, *p*-MeC_6H_4 (1)	0.5	24 h	**2.13f**, 31

*: **13a** in acetonitrile; the rests in ethanol.

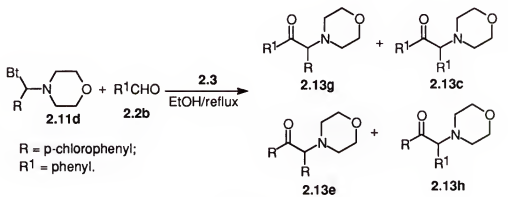


Figure 2.9

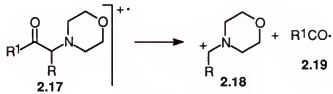


Figure 2.10

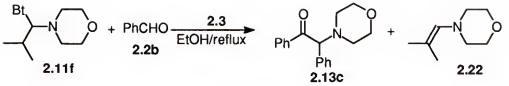


Figure 2.11

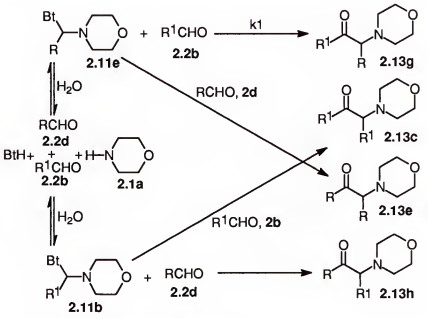


Figure 2.12

Different cross-over ratios among the four possible products were found between R^1 = *p*-cyanophenyl (**2.2c**), R = Ph (**2.11b**); R^1=Ph (**2.2b**), R = *p*-methoxyphenyl (**2.11c**); and even R^1 = Ph (**2.2b**), R = *i*-Pr (**2.11f,** Figure 2.11). No cross-over was detected in the reaction between R^1=*p*-cyanophenyl (**2.2c**), R = *p*-methoxyphenyl (**2.11c**). Figure 2.11 also reveals that β-H elimination of benzotriazole may overwhelm other processes if the benzotriazolyl adduct **2.11** contains an β-hydrogen.

The cross-over process is interpreted in Figure 2.12. When the desired reaction k1 is fast enough to overwhelm other pathways, no cross-over should be observed, which is the case with entry 4 in Table 2.7. A trace of water in the reaction mixture may be responsible for the catalysis of the exchange of R^1 and R.

2.3 Experimental

General

Melting points were determined using a Thomas Hoover capillary Melting Point Apparatus and are not corrected. NMR spectra were recorded on a Varian Gemini-300 spectrometer at 75 MHz for ^{13}C and 300 MHz for ^{1}H using either deuteriochloroform or dimethyl sulfoxide-d_6 as solvent. Chemical shift values are reported as δ downfield from TMS as an internal standard. The GC-MS instrument used was a Hewlett Packard 5890 Series II Gas Chromatography coupled to a 5972 Mass Selective Detector. Elemental analyses were performed on a Carlo Erba-1106 instrument. The aldehydes, triethylamine, ammonium chloride and solvents were from commercial sources. Anhydrous solvents and nitrogen as protecting atmosphere were preferred in the preparation of the α-amino ketones **2.13**. The catalyst 3-benzyl-4,5-dimethylthiazolium chloride (**2.3**) was prepared by refluxing 4,5-dimethylthiazole and benzyl chloride in acetonitrile. *N*-Morpholinomethylbenzotriazole (**2.11a**) [89H1121], α-phenyl-(*N*-morpholino)methylbenzotriazole (**2.11b**) [89JCS(P1)225], α-(*p*-methoxyphenyl)-(*N*-morpholino)methylbenzotriazole (**2.11c**) [89H1121] were prepared according to literature methods. Compounds **2.11d,e** (Table 2.7) were prepared as outlined below.

Procedure for Preparation of Compounds **2.11d,e**

A mixture of benzotriazole (2.38 g, 20 mmol), morpholine (1.74 g, 20 mmol) and the aldehyde **2.2d,e** (20 mmol) was refluxed in benzene (100 mL) with a Dean-Stark trap until the calculated amount of water had been collected. The solvent was removed under reduced pressure and the residue redissolved in CH_2Cl_2, washed with 10% Na_2CO_3 (2 × 40 mL) and water (2 × 40 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness to give the product **2.11d,e**.

p-Chlorophenyl-(*N*-morpholino)methyl-benzotriazole (**2.11d**). (81%, as a mixture of Bt1 and Bt2 isomers): oil; ^{1}H NMR δ 2.50-3.00 (m, 4 H), 3.60-3.90 (m, 4 H), 6.66 (Bt1 isomer) and 6.71 (Bt2 isomer) (s, 1 H), 7.10-8.11 (m, 8 H). Anal. Calcd for $C_{17}H_{17}N_4OCl$: C, 62.10; H 5.18; N, 17.05. Found: C, 62.36; H, 5.25; N, 17.08.

p-Methylphenyl-(*N*-morpholino)methylbenzotriazole (**2.11e**). (80%, as a mixture of Bt1 and Bt2 isomers): mp 113-114 °C; ^{1}H NMR δ 2.34 (s, 3 H), 2.58-2.62 (Bt1 isomer) and 2.80-2.92 (Bt2 isomer) (m, 4 H), 3.73-3.77 (m, 4 H), 6.64 (Bt1 isomer) and 6.70 (Bt2 isomer) (s, 1 H), 7.13-8.10 (m, 8 H). Anal. Calcd for $C_{18}H_{20}N_4O$: C, 70.13; H 6.49; N, 18.18. Found: C, 69.80; H, 6.52; N, 18.31.

General Procedure for Preparation of α-Amino Ketones **2.13a-f**. Typical Procedure for the Preparation of 3-Methyl-1-(*N*-Morpholino)-2-butanone (**2.13a**)

A solution of the thiazolium salt **2.3** (0.6 g, 2.5 mmol), benzotriazolyl compound **2.11a** (0.55 g , 2.5 mmol) and isobutyraldehyde **2.2a** (0.36 g, 5.0 mmol) in acetonitrile (20 mL) was refluxed under nitrogen for 72 h. The solvent was evaporated, the residue redissolved in CH_2Cl_2 and washed with 10% Na_2CO_3 (3 × 30 mL). The mixture was extracted with 10 M HCl (3 × 30 mL), neutralized with 30% NH_4Cl and extracted with CH_2Cl_2 (2 × 60 mL). Evaporation of the solvent yielded a residue which was subjected to

flash chromatography (CH_2Cl_2/acetone 10:1) followed by distillation to give **2.13a** as an oil (0.71 g, 28%): bp 50 °C/0.5mm, lit. bp 77-78 °C/2mm [78MI517]; ^{1}H NMR ($CDCl_3$) δ 1.10 (d, *J* = 6.9 Hz, 6 H), 2.50 (t, *J* = 4.5 Hz, 4 H), 2.71 (septet, *J* = 7.0 Hz, 1 H), 3.27 (s, 2 H), 3.76 (t, *J* = 4.5 Hz, 4 H). ^{13}C NMR ($CDCl_3$) δ 18.2, 38.5, 53.7, 65.8, 66.7, 211.5. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.1; H 10.0; N, 8.2. Found: C, 62.9; H, 9.9; N 8.2.

α-(*N*-Morpholino)acetophenone (**2.13b**). The title compound was prepared as above from benzotriazolyl compound **11a** (0.55 g, 2.5 mmol), thiazolium salt **2.3** (0.06 g, 0.25 mmol) and benzaldehyde **2.2b** (0.53 g, 5.0 mmol) except that the reaction was refluxed for 8 h. Distillation gave **2.13b** as a solid (0.30 g, 58%): mp 78-81 °C; bp 124°C/1mm. ^{1}H NMR ($CDCl_3$) δ 2.62 (t, *J* = 4.5 Hz, 4 H), 3.78 (t, *J* = 4.7 Hz, 4 H), 3.83 (s, 2 H), 7.45 (m, 2 H), 7.57 (m, 1H), 8.00 (d, *J* = 6.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ 53.8, 64.7, 66.8, 128.0, 128.5, 133.2, 136.0, 196.0. Anal. Calcd for $C_{12}H_{12}NO_2$: C, 70.2; H 7.4; N, 6.8. Found: C, 69.9; H, 7.3; N 7.0.

α-(*N*-Morpholino)-α-phenylacetophenone (**2.13c**). The title compound was prepared as above from benzotriazolyl compound **2.11b** (2.94 g, 10.0 mmol), thiazolium salt **3** (0.24 g, 1.0 mmol) and benzaldehyde **2.2b** (2.12 g, 20.0 mmol) except that the reaction was refluxed for 20 h. Flash chromatography (dichloromethane/acetone 20:1) followed by trituration with ether gave **2.13c** (1.24 g, 44%): mp 79-81°C, lit. mp 78 °C [70BSC1926]; ^{1}H NMR ($CDCl_3$) δ 2.52 (m, 4 H), 3.76 (m, 4 H), 4.94 (s, 1 H), 7.28-7.45 (m, 8 H), 8.01 (d, *J* = 7.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ 52.2, 66.9, 76.5, 128.4, 128.7, 128.8, 129.7, 133.1, 134.7, 136.5, 197.3. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.8; H 6.8; N, 5.0. Found: C, 76.5; H, 6.8; N 5.0.

α-(*p*-Methoxyphenyl)-α-(*N*-morpholino)-*p*-cyanoacetophenone (**2.13d**). The title compound was prepared as above from benzotriazolyl compound **2.11c** (1.80 g, 5.6 mmol), thiazolium salt **3** (0.66 g, 2.8 mmol) and 4-cyanobenzaldehyde **2.2c** (0.36 g, 2.8 mmol) except that the reaction was refluxed for 6 h. Flash chromatography (dichloromethane/acetone 20:1) gave **2.13d** as an oil (0.39 g, 42%): oil; ^{1}H NMR ($CDCl_3$)

δ 2.50 (m, 4 H), 3.75 (m, 4 H), 3.76 (s, 3 H), 4.81 (s, 1 H), 6.84 (d, J = 8.9 Hz, 2 H), 7.27 (d, J = 8.8 Hz, 2 H) 7.68 (d, J = 8.7 Hz, 2 H), 8.07 (d, J = 8.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ 52.0, 55.2, 66.8, 114.6, 116.2, 117.8, 125.2, 129.0, 130.9, 132.3, 139.5, 159.9, 196.0. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.4; H 6.0; N, 8.3. Found: C, 71.3; H, 6.1, N 8.3.

α-(*p*-Chlorophenyl)-α-(*N*-morpholino)-*p*-chloroacetophenone (**2.13e**). The title compound was prepared as above from benzotriazolyl compound **2.11d** (2.50 g, 7.6 mmol), thiazolium salt **2.3** (0.85 g, 3.6 mmol) and 4-chlorobenzaldehyde **2.2d** (2.13 g, 15.2 mmol) except that the reaction was refluxed for 24 h. Flash chromatography (CH_2Cl_2/acetone 20:1) and trituration with ether gave **2.13e** as an oil (1.45 g, 55%): ^{1}H NMR ($CDCl_3$) δ 2.49 (m, 4 H), 3.74 (m, 4 H), 4.83 (s, 1 H), 7.27-7.40 (m, 8 H), 7.97 (d, J = 8.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ 52.0, 66.8, 76.0, 128.9,129.2, 130.1, 130.8, 133.0, 134.4, 134.5, 139.9, 195.8. Anal. Calcd for $C_{18}H_{17}NO_2Cl_2$: C, 61.9; H 4.90; N, 4.00. Found: C, 61.9; H, 4.90; N 4.00.

α-(*p*-Methylphenyl)-α-(*N*-morpholino)-*p*-methylacetophenone (**2.13f**). The title compound was prepared as above from benzotriazolyl compound **2.11e** (1.84 g, 6.0 mmol), thiazolium salt **3** (0.71 g, 3.0 mmol) and 4-methylbenzaldehyde **2.2e** (1.43 g, 11.9 mmol) except that the reaction was refluxed for 24 h. Flash chromatography (CH_2Cl_2/acetone 20:1) gave **2.13f** as an oil (0.58 g, 30%): ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.34 (s, 3H), 2.50 (m, 4H), 3.75 (m, 4H), 4.86 (s, 1H), 7.09-7.32 (m, 8H), 7.92 (d, J = 8.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ 21.0, 21.5, 52.2, 99.9, 76.1, 127.2, 128.8, 129.1, 129.1, 129.5, 138.1, 143.8, 296.8. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.6; H 7.4; N, 4.5. Found: C, 77.5; H, 7.6; N 4.9.

2,2-Dimethyl-3-(*N*-morpholino)propionaldehyde (**2.14**). A mixture of paraformaldehyde (0.60 g, 20.0 mmol) and morpholine (1.74 g, 20.0 mmol) in ethanol (20 mL) was refluxed until a clear solution was obtained. The mixture was cooled and isobutyraldehyde (2.88 g, 40.0 mmol) and triethylamine (0.40 g, 4.0 mmol) was added and the solution refluxed for 8 h. The reaction was worked up as above (see Preparation of **2.13a**). The

residue was subjected to column chromatography (dichloromethane/acetone 20:1) to give **2.14** as an oil (1.85 g, 54%): bp 55 °C/0.5 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 6H), 2.46 (t, *J* = 4.7 Hz, 4 H), 2.48 (s, 2 H), 3.27 (s, 2 H), 3.64 (t, *J* = 4.7 Hz, 4 H) 9.56 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 20.5, 47.4, 55.2, 65.5, 67.0, 206.2. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.1; H 10.0; N, 8.2. Found: C, 62.8; H, 10.1; N 8.2.

GC-MS data for identification of the cross-over products between benzaldehyde **2.2b** and *p*-Chlorophenyl-(*N*-morpholino)methyl-benzotriazole **2.11d**. M^+ = 281, base peak = 176 (**2.13c**); M^+ = 315, base peak = 176 (**2.13h**); M^+ = 315, base peak = 210 (**2.13g**); M^+ = 349, base peak = 210 (**2.13e**).

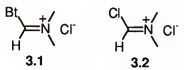
Applying the "No-base-added" Conditions to the Literature [88S314] Method

A mixture of morpholine **2.1a** (1.74g, 20 mmol), paraformaldehyde (0.6g, 20 mmol) and dry EtOH (30 mL) was refluxed until the paraformaldehyde had dissolved (1 h). Benzaldehyde **2.2b** (2.12g, 20 mmol) and thiazolium salt **2.3** (0.24g, 2.0 mmol) were added. and the mixture was refluxed for 8 h. The solvent was evaporated and the residue redissolved in CH_2Cl_2 (50 mL). This solution was washed with water until the aqueous layer was neutral. The solution was then extracted with 5N HCl (2 x 75 mL). The extract was neutralized with NH_3/H_2O and extracted with CH_2Cl_2 (2 x 50 mL). The CH_2Cl_2 extract was dried (Na_2SO_4) and the solvent evaporated. The oily residue was distilled under reduced pressure to give product (1.19g, 52%) which was the identical to the product **2.13b** obtained by benzotriazole-mediated synthesis described above.

CHAPTER 3
STUDY OF *N,N*-DIMETHYLBENZOTRIAZOLYL-METHYLENEIMINIUM CHLORIDE

3.1 Introduction

Iminium salts constitute an important part in organic chemistry [79MI1]. Examples include Eschenmoser's salt [71AG330] and Vilsmeier reagents [79MI1], which have been used widely in organic synthesis. (*N,N*-Dialkylaminoalkyl)benzotriazoles have been used successfully as generalized iminium ion equivalents in many cases [91T2683], and Chapter 2 shows the example of the use of such a generalized iminium ion equivalent in the synthesis of α-amino ketones. The present Chapter reports the study of the reactivity of the title compound **3.1** (Figure 3.1) towards nucleophiles (directed towards its potential as a stable substitute for the Vilsmeier reagent **3.2**) and to electrophiles under mild basic conditions (on generation of the nucleophilic *N,N*-dimethyl-aminobenzotriazolylcarbene **3.3**).



3.1 **3.2**

Figure 3.1

As shown in Figure 3.1, compound **3.1**, *N,N*-dimethylbenzotriazolyl-methyleneiminium chloride, structurally resembles the Vilsmeier reagent **3.2**. Since both chlorine atoms and Bt groups are good leaving groups, it is anticipated that compound **3.1**

and the Vilsmeier reagent **3.2** are chemically similar. Vilsmeier reagents have extensive use in organic synthesis [79MI1]. Representative applications include formylation (as in Vilsmeier-Haack reaction [70JCS(C)2563]), chlorination [69TL165], dimethylamino-methylenation [83S195], preparation of other more stable iminium salts [78HCA1675] and *N,N*-dimethylformamide derivatives [72TL4217], synthetic transformations by activating oxygen-containing functional groups [65TL1321] [79MI1] [83CL1537] [83TL1543], *etc.* Because of their high reactivity, Vilsmeier reagents are normally generated *in situ*. However, there are some cases where isolated reagents are necessary [62TL397] [93SC2199]. Considering that the Bt group can further stabilize the cation with its electron donation and that a Bt group is usually not as good a leaving group as a chlorine atom, salt **3.1** is expected to be more stable than the Vilsmeier reagent **3.2**. Hence, compound **3.1** was first studied for its potential as a more stable substitute for the Vilsmeier reagent **3.2**.

In the study of compound **3.1**, it was found that it dimerized in the presence of triethylamine, which suggested the formation of *N,N*-dimethylaminobenzotriazolylcarbene **3.3** (Figure 3.2). Therefore, the study of compound **3.1** was shifted to trapping the nucleophilic carbene **3.3**.

3.3

Figure 3.2

Carbenes connected directly to heteroatoms (*N, O, S, etc.*) are of enduring interest [71JHC551] [80ACR58] [84TL1023] [89ACR15]. Among these so-called "nucleophilic carbenes", aminocarbenes are of uniquely high stability and low reactivity [80ACR58] [80JACS1770]. For example, cyclopropanation which is typical of normal carbenes, has rarely been seen with aminocarbenes and questions remain about the structure of the

isolated product in the case reported [62AG(I)75]. In comparison, cyclopropanation is very common with oxocarbenes [76JCS(C)950] [87JACS3811] [87JACS4341]. The high stability of aminocarbenes have been evidenced recently by the isolation and X-ray structure determination of some special structures [91JACS361] [92JACS5530] [95AG(E)1021] [95JACS11027]. Heterocyclic aminocarbenes have been found to react with electrophiles including aldehydes, benzoyl halides, alkyl halides, phenyl isothiocyanate, and cyclopentanone [62AG(E)75] [70CB1037] [75TL1889]. However, the few reported reactions of acyclic nucleophilic carbenes were limited to [1+2+2] cycloadditions with aryl isocyanates and isothiocyanates [77CB37] and [1+4] cycloadditions with tetrazines [93CB733].

Herein is reported the generation of a new acyclic aminocarbene, *N,N*-dimethyl-aminobenzotriazolylcarbene (**3.3**), by deprotonation of *N,N*-dimethylbenzotriazolyl-methyleneiminium chloride (**3.1**) under mild conditions. This carbene has been trapped with *trans*-dibenzoylethylene (**3.25**) in a [1+4] cycloaddition (Scheme 3.10) and with phenyl isocyanate (**3.22**) in reactions which demonstrate some synthetic utility in approaching the hydantoin system **3.24a-g** (Scheme 3.9).

3.2 Results and Discussions

Preparation and Characterization of *N,N*-Dimethylbenzotriazolylmethyleneiminium Salt (**3.1**)

N,N-Dimethylbenzotriazolylmethyleneiminium chloride (**3.1**) has been prepared as a hygroscopic white solid in high yields by either of the two methods shown in Figure 3.3.

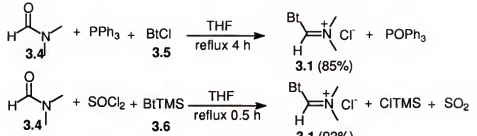


Figure 3.3

Although no systematic effort has been made to date to comparing the stability of the salt **3.1** with Vilsmeier reagents, salt **3.1** appears to be easily isolable and easy to handle as a shelf-compound. In contrast, corresponding Vilsmeier reagent **3.2** (Figure 3.1) is hardly isolable. According to the writer's experience, it was a solid under vacuum, but once the vacuum was removed, it immediately collapsed into a sticky liquid.

Like Vilsmeier reagent **3.2**, compound **3.1** is sensitive to water because of its strong propensity to decompose back to DMF **3.4**, which makes it difficult to characterize. Its ^{1}H and ^{13}C NMR spectra appeared like a one to one mixture of benzotriazole and DMF (addition of pure DMF (**3.4**) to DMSO-d_6 solution of the salt **3.1** showed no new peaks on the spectra and only the changes of integration ratio were observed). The explanation is that compound **3.1** decomposed by reaction with the water contained in DMSO-d_6 to benzotriazole and DMF. Fortunately, elemental analysis proved the correct formula. Its similar chemical properties to Vilsmeier reagents shown below also serve to confirm its structure.

Reactions of *N,N*-Dimethylbenzotriazolylmethyleneiminium Chloride (**3.1**) with Nucleophiles as a Potential Stable Substitute for the Vilsmeier Reagent **3.2**.

Compound **3.1**, as anticipated, showed the same reaction patterns as those of the Vilsmeier reagents (*N,N*-dialkylchloromethyleneiminium salts) in all the cases investigated.

i). Synthesis of dimethylformamide derivatives

Compound **3.1** was used to synthesize 2-dimethylamino-benzo-1,3-dioxole (**3.8**) to compare with a literature method using compound **3.2** generated *in situ* [72TL4217]. (Scheme 3.4).

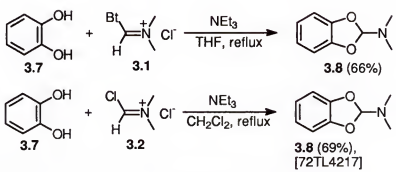


Figure 3.4

ii). *N,N*-Dimethylaminomethylenation

N,N-dimethylaminomethylenation was attempted with dimethyl malonate to compare with similar reported transformations [83S195] (Figure 3.5).

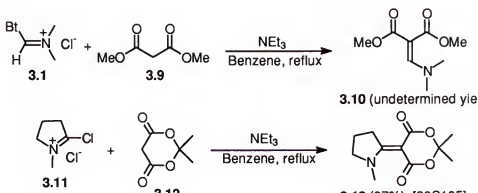


Figure 3.5

iii). Activation of oxygen-containing functional groups

Transformations in this category including activation of carboxylic acids to give acid chlorides, esters, acyl azides, aldehydes, activation of epoxy groups to give chlorinated esters, and activation of nitro compounds to give ketoximes, *etc* [79MI1] [65TL1321] [83CL1537] [83CL1543], have been achieved by using Vilsmeier reagents. Compound **3.1** was used to synthesize ketoximes **3.16** in order to compare with *N,N*-dimethyl-chloromethyleneiminium chloride (**3.2**) generated *in situ* (Figure 3.6). The intermediate, ethyl benzotriazol-2-yl ketoxime (**3.15**), was isolated and the one-pot reaction mixture gave the same characteristic ethyl peaks in ^{1}H NMR spectrum as those of the reaction mixture obtained by repeating the literature method [83TL1537] and the expected the molecular ion peak was detected by GC-MS. Unfortunately, the pure final product **3.16** has not been successfully isolated.

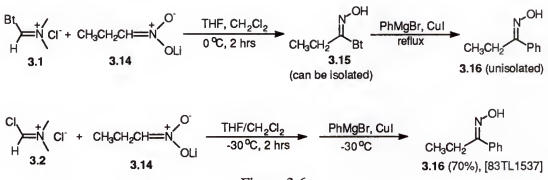


Figure 3.6

iv). Formylation

Formylation was the classical synthetic use of Vilsmeier reagents, and has been applied beyond Vilsmeier-Haack reactions to olefins and enamines [79MI1]. Figure 3.7

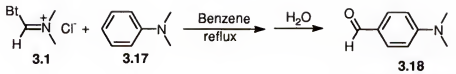


Figure 3.7

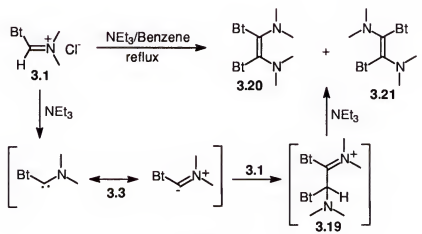


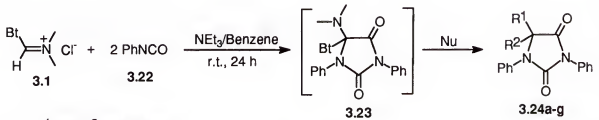
Figure 3.8

shows the results of using compound **3.1** to formylate activated benzene rings **3.17**. Comparing the two yields by using different amounts of the substrate **3.17** (Figure 3.7), it is believed that protonation of the substrate by the HCl evolved during the reaction deactivated the ring and thus caused the low yield. Thus the reaction was attempted with one equivalent of *N,N*-dimethylaniline **3.17** in the presence of one equivalent of triethylamine. Surprisingly, this resulted in the formation of the dimeric compounds **3.20** and **3.21**. This can be explained by the formation of the corresponding aminocarbene **3.3** (Figure 3.8). Interestingly, Y. Cheng *et al* noticed the unexpected formation of aminocarbenes from Vilsmeier reagents [96JCS(C)1395] [96TL9381] at about the same time as carbene **3.3** was found.

Generation of Dimethylaminobenzotrizolylcarbene (**3.3**) and Study on its Reactivity

Further evidence for the formation of the new aminocarbene **3.3** was given by treating **3.1** with phenyl isocyanate **3.22** in a known [1+2+2] cycloaddition of nucleophilic carbenes [77CB37] (Figure 3.9). However, imidazolidinetrione (**3.24a**) (Table 3.1) was isolated instead of the expected 5-dimethylamino-5-benzotriazolyl-1,3-diphenylhydantoin (**3.23**). The Bt group is evidently easily substituted, and thus the proposed intermediate **3.23** is hydrolyzed on work-up to the corresponding oxo-derivative **3.24a**.

Quenching this reaction with various nucleophiles enabled the one-pot synthesis of various 5-substituted hydantoins **3.24a-g** (Table 3.1) in acceptable yields by using simple reagents under mild conditions.



For R^1 and R^2, see Table 3.1

Figure 3.9

Table 3.1. Preparation of Hydantoins **3.24a-g**

Entry	Nu	R^1	R^2	**3.24**	Yield (%)
1	H_2O	carbonyl		**a**	67
2	propylamine	propylimino		**b**	54
3	NEt_4HS	H	H	**c**	35
4	MeOH	dimethylamino	MeO	**d**	57
5	Morpholine	dimethylamino	N-morpholinyl	**e**	48
6	$NaBH_4$	dimethylamino	H	**f**	51
7	EtMgBr	dimethylamino	Et	**g**	56

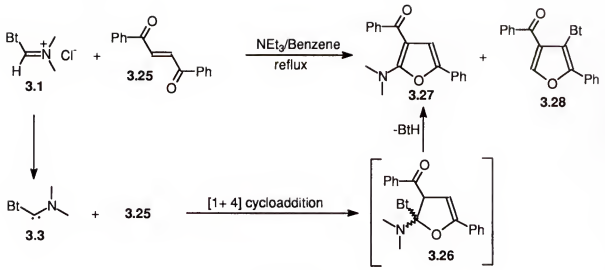


Figure 3.10

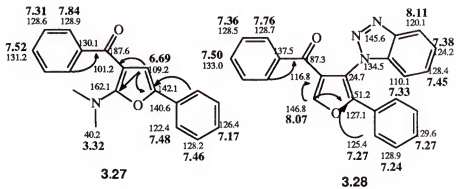


Figure 3.11

Apart from the known reaction to trap the carbene **3.3** discussed above, it was found that *trans*-dibenzoylethylene **3.25** could react with carbene **3.3** to give a 15% yield of the 2-dimethylamino-3-benzoyl-5-phenylfuran (**3.27**) and a 6% yield of 2-pheny-3-benzotriazolyl-4-benzoylfuran (**3.28**) after refluxing for 24 hours (Figure 3.10). The structures of furans **3.27** and **3.28** were assigned on the basis of the ^{1}H-^{13}C direct and long range correlations and ^{13}C chemical shifts (performed by Dr. I. Ghiviriga). The chemical shifts and the relevant ^{1}H-^{13}C long range correlations for compounds **3.27** and **3.28** are given in Figure 3.11. The formation of the 2-dimethylamino-3-benzoyl-5-phenylfuran (**3.27**)

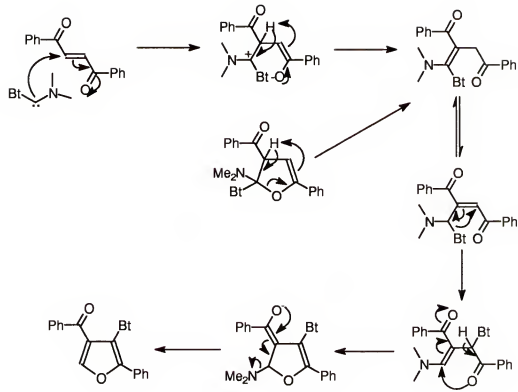


Figure 3.12

can be easily explained by a carbene mechanism as shown in Figure 3.10. Such [1+4] cycloadditions with unsaturated carbonyl compounds are common with isocyanides [82JOC741] and have occasionally been reported as side-reactions of the cyclopropanation of sulfoxonium ylides [79TL1207]. Hoffmann and co-workers have reported similar reactions of dimethoxycarbene with special heterodienes [76CB1579]. A stepwise ionic cycloaddition seems more likely than a concerted mechanism in the light of orbital considerations and previous results on cycloaddition of "nucleophilic" carbenes [77CB37] [93CB733] [70JCS(C)907] [73CB2174].

The formation of 2-phenyl-3-benzotriazolyl-4-benzoylfuran (**3.28**), its structure confirmed by X-ray crystallography (Figure 3.12, see experimental), was initially believed to have resulted from reaction of 2-dimethylamino-3-benzoyl-5-phenylfuran (**3.27**) with free benzotriazole. This assumption was made on the basis that when monitoring the reaction by

GCMS, the peak corresponding to compound **3.28** appeared after 18 hours and was observed to increase in size while the peak corresponding to compound **3.27** decreased. However, this hypothesis was rejected because **3.27** was unchanged by refluxing in benzene with benzotriazole in the presence of one equivalent of triethylamine for 72 hours. A possible mechanism leading to compound **3.28** is shown in Figure 3.12 (proposed by Dr. Leeming and Dr. Katritzky).

3.3 Experimental

General

Melting points were determined using a Thomas Hoover capillary Melting Point Apparatus and were not corrected. NMR spectra were recorded on a Varian Gemini-300 spectrometer at 75 MHz for ^{13}C and 300 MHz for ^{1}H using either deuteriochloroform or dimethyl sulfoxide-d_6 as solvent. Chemical shift values are reported as δ downfield from TMS as an internal standard. The GCMS instrument used was a Hewlett Packard 5890 Series II Gas Chromatography coupled to a 5972 Mass Selective Detector. Elemental analyses were performed on a Carlo Erba-1106 instrument. 1-Chlorobenzotriazole **3.5** [69JCS(C)1474] and 1-trimethylsilylbenzotriazole (**3.6**) [68JHC785] were prepared according to literature methods. Tetrahydrofuran and benzene was predried and freshly distilled from sodium and benzophenone. Methylene chloride and dimethylformamide (**3.4**) were dried over molecular sieves. Column chromatography was carried out on MCB silica gel (230-400 mesh). Reactions were carried out under dry nitrogen with magnetic stirring.

Preparation of *N,N*-Dimethylbenzotriazolylmethyleneiminium Chloride (**3.1**)

Procedure **A**: A solution of DMF (**3.4**) (7.4 g, 100 mmol) and triphenylphosphine (26.2 g, 100 mmol) in dry THF (100 mL) was treated with a solution of 1-chlorobenzotriazole (**3.5**) (15.4 g, 100 mmol) in dry THF (40 mL), dropwise. The mixture was then refluxed for 4 h before cooling and filtering off the resulting precipitate, which was washed once with dry THF (40 mL) to give product **3.1** as a white solid (17.9 g, 85%).

Procedure **B**: To a solution of 1-trimethylsilylbenzotriazole (**3.6**) (10.7 g, 55.2 mmol), DMF (**3.4**) (4.08 g, 55.2 mmol) and dry THF (100 mL) was added thionyl chloride (4.0 mL, 55.2 mmol) dropwise. The mixture was then refluxed 30 min before cooling and filtering off the resulting precipitate, which was washed once with dry THF (40 mL) to give product **3.1** as a white solid (10.6 g, 92%): Anal. Calcd. for $C_9H_{11}ClN_4$ (210.5): C, 51.41; H, 5.28; N, 26.66. Found: C, 51.18; H, 5.24; N 26.67.

Comparing Compound **3.1** with Vilsmeier Reagents

2-Dimethylaminobenzo-1,3-dioxole (**3.8**) To a flask containing *N,N*-dimethylbenzotriazolylmethyleneiminium chloride **3.1** (1.06 g, 5 mmol), dry THF (30 mL) and catechol **3.7** (0.55 g, 5 mmol), was added dropwise triethylamine (1.01 g, 10 mmol). The mixture was refluxed for 1 h. After it was cooled down, the mixture was filtered and washed with dry ether. Evaporation of the solvents followed by vacuum distillation gave product **3.8** as an oil (0.54 g, 66%): bp 69 °C/0.7 mmHg, lit. bp 61 °C/0.5 mmHg [72TL4217]; ^{1}H NMR δ 2.49 (s, 6 H), 6.63 (s, 1 H), 6.80 (br s, 4 H); ^{13}C NMR 36.1, 107.7, 118.7, 121.0, 147.1.

Dimethyl (dimethylaminomethylene)propanedioate (**3.10**) To a flask containing *N,N*-dimethylbenzotriazolylmethyleneiminium chloride **3.1** (1.06 g, 5 mmol), dimethyl malonate (0.66 g, 5 mmol) and dry benzene (25 mL) was added triethylamine (0.50 g, 5 mmol)

dropwise. The mixture was refluxed overnight and filtered after it was cooled to room temperature and filtered. The organic layer was washed with 10% Na_2CO_3 (20 mL) and water (20 mL) and dried with Na_2SO_4. Evaporation of the solvent gave an oil which crystallized upon triturated with ether/hexane (undetermined yield): mp 65-67 °C, lit mp 65-67 °C [69JACS6683]; ^{1}H NMR δ 3.00 (s, 6 H), 3.71 (br s, 3 H), 3.77 (br s, 3 H), 7.55 (s, 1 H); ^{13}C NMR 51.3, 51.5, 92.1, 154.0, 167.7.

Benzotriazol-2-yl ethyl ketoxime (**3.15**) To a suspension of *N,N*-dimethylbenzotriazolylmethyleneiminium chloride **3.1** (1.26 g, 6 mmol) in dry methylene chloride (30 mL) at 0 °C, was added the lithium salt of aci-nitropropane (0.54 g, 6 mmol), prepared by mixing with 1 eq of butyl lithium in dry THF (30 mL) at -78 °C for 15 min. The mixture was stirred for 2 h at 0 °C before it was worked up with saturated NH_4Cl solution (75 mL) and washed with water (2 x 50 mL) and dried with Na_2SO_4. After evaporation of the solvents, the residue was subjected to silica gel column chromatography with ethyl acetate/hexane (1:1) as eluent to give **3.15** as an oil (0.48 g, 50%): ^{1}H NMR δ 1.40 (t, J = 7.5 Hz, 3 H), 3.19 (q, J = 7.5 Hz, 2 H), 7.52-7.56 (m, 2 H), 7.92-7.95 (m, 2 H), 13.17-13.19 (m, 1 H); ^{13}C NMR 11.0, 25.4, 118.3, 129.1, 142.3, 143.4. Anal. Calcd for $C_9H_{10}N_4O$ (348): C, 56.84; H, 5.26; N, 29.47. Found: C, 56.76; H, 5.30; N, 29.70.

cis- and *trans*-1,2-Bis[1-benzotriazolyl]-1,2-bis(dimethylamino)ethylene (**3.20**) and (**3.21**) Compound **3.1** (1.06 g, 5.0 mmol) in dry benzene (20 mL) was refluxed in the presence of an equimolar of triethylamine overnight. The mixture was then washed with water (2 x 20 ml), dried over anhydrous $MgSO_4$, filtered and then evaporated to dryness to give an oily residue which was subjected to column chromatography. From the column it was possible to obtain some fractions that contained pure **3.20** (oil) and **3.21** (oil), the other fractions being mixtures of the two geometrical isomers with an overall yield of 45%. ^{1}H NMR of the reaction mixture showed that the ratio between **3.20** and **3.21** was about 1:1.

3.20 ^{1}H NMR ($CDCl_3$): δ 2.83 (s, 12 H), 7.19 (t, J = 7.2 Hz, 2 H), 7.36 (t, J = 8.1 Hz, 2 H), 7.55 (d, J = 8.3 Hz, 2 H), 7.77 (d, J = 9.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$): δ 40.71,

110.33, 119.54, 124.06, 125.16, 127.93, 132.93, 144.97; Anal. Calcd for $C_{18}H_{20}N_8$: C, 62.04; H, 5.79; N, 32.17. Found: C, 62.11; H, 5.69; N, 31.90.

3.21 ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 12 H), 7.47 (t, *J* = 8.2 Hz, 2 H), 7.58 (t, *J* = 8.1 Hz, 2 H), 7.73 (d, *J* = 8.2 Hz, 2 H), 8.16 (d, *J* = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$): δ 40.18, 110.95, 120.18, 124.49, 125.29, 128.29, 133.56, 146.01. Anal. Calcd for $C_{18}H_{20}N_8$: C, 62.04; H, 5.79; N, 32.17. Found: C, 62.28; H, 5.76; N, 31.88.

General Procedure for the Synthesis of 5-Substituted-1,3-diphenylhydantoins **3.24a-g**.

A mixture of **3.1** (1.06 g,, 5.0 mmol), phenyl isocyanate **3.22** (1.19 g, 10.0 mmol) and triethylamine (1.01 g, 10 mmol) in dry benzene (20 mL) was stirred 24 h at room temperature. This was then quenched with the corresponding nucleophile to give the products **3.24a-g**.

1,3-Diphenylimidazolidinetrione (**3.24a**) The reaction mixture was quenched with water (20 mL), heated to reflux, cooled and extracted with diethyl ether (30 mL). The organic extracts were washed with water (2 x 40 ml), dried over anhydrous $MgSO_4$, filtered and evaporated to dryness to give an oily residue. This was then treated with ethanol and refrigerated to crystallize out the product **3.24a** as a white solid (0.89 g, 67%): mp 204-205 °C, lit. mp 206-207 °C [67JOC383]; ^{1}H NMR ($CDCl_3$): δ 7.40-7.60 (m, 10 H); ^{13}C NMR ($CDCl_3$): δ 125.84, 129.25, 129.51, 129.74, 151.76, 155.03.

5-Propylimino-1,3-diphenylhydantoin (**3.24b**) The reaction mixture was cooled to 0 °C before adding a solution of propylamine (10 mmol) in dry benzene (3 mL), dropwise. This was then stirred at room temperature for 30 min before cooled to 0 °C and filtered off the resulting precipitate. Evaporation of the filtrate gave an oil which was subjected to column chromatography with ethyl acetate/hexane (1:1) as the eluent to give the product **3.24b** as an oil (0.83 g, 54%): ^{1}H NMR ($CDCl_3$): δ 0.99 (t, *J* = 7.4Hz, 3H), 1.71 (sextet, *J* = 7.1Hz, 2H), 4.16 (t, *J* = 7.0Hz, 2H), 7.35-7.60 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 11.81,

24.45, 51.58, 126.13, 127.14, 128.09, 128.63, 128.94, 129.16, 130.44, 131.88, 140.32, 152.11, 154.08; HRMS Calcd for $C_{18}H_{17}N_3O_2$ m/e 307.1321. Found: 307.1321.

1,3-Diphenylhydantoin (**3.24c**) The reaction mixture was quenched with tetraethylammonium hydrogensulfide (20 mmol) and then stirred overnight. This was then cooled to 0 °C, filtered and then diluted with diethyl ether (30 mL) before washing with water (2 x 40 ml), drying over anhydrous $MgSO_4$, filtering and evaporating to dryness. The resulting product was subjected to column chromatography with ethyl acetate/hexane (1:1) as eluent to give the solid product **3.24c** (0.44 g, 35%): mp 136-137 °C lit. mp 135 °C [61AG434]; ^{1}H NMR ($CDCl_3$): δ 4.40 (s, 2 H), 7.13-7.21 (m, 1 H), 7.35-7.52 (m, 7 H), 7.60 (d, *J* = 7.7Hz, 2 H); ^{13}C NMR ($CDCl_3$): δ 49.59, 118.46, 124.52, 126.19, 128.33, 129.01, 129.24, 131.23, 137.35, 153.04; 167.24.

5-Methoxy-5-dimethylamino-1,3-diphenylhydantoin (**3.24d**) The reaction mixture was quenched with methanol (2 mL) and then heated to reflux before cooling to 0 °C and filtering off the resulting precipitate. Evaporation of the filtrate gave an oily residue which was treated with methanol and refrigerated to crystallize out the product **3.24d** as a white solid (0.93 g, 57%): mp 140 °C, lit. mp 140 °C [71CH3794]; ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 6 H), 3.49 (s, 3 H), 7.23-7.31 (m, 1 H), 7.37-7.54 (m, 7 H), 7.73 (d, J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$): δ 37.54, 51.82, 101.21, 124.27, 126.26, 126.47, 128.49, 128.88, 129.10, 130.70, 134.33, 152.77, 166.72.

5-(*N*-Morpholinyl)-5-dimethylamino-1,3-diphenylhydantoin (**3.24e**) The reaction mixture was quenched with morpholine (2 mL) and then heated to reflux before cooled to 0 °C and filtered off the resulting precipitate. Evaporation of the filtrate gave an oily residue which was treated with methanol and refrigerated to crystallize out the product **3.24e** as a white solid (0.91 g, 48%): mp 194 °C; ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 6 H), 2.60-2.72 (m, 2 H), 3.02-3.13 (m, 2 H), 3.70-3.83 (m, 4 H), 7.28-7.36 (m, 1 H), 7.36-7.55 (m, 7 H), 7.59 (d, *J* = 8.2Hz, 2 H); ^{13}C NMR ($CDCl_3$): δ 37.77, 46.75, 67.02, 95.50, 126.32, 126.73,

127.36, 128.37, 129.04, 131.10, 136.00, 153.39, 167.66. Anal. Calcd for $C_{21}H_{24}N_4O_3$: C, 66.28; H, 6.36; N, 14.73. Found: C, 66.49; H, 6.36; N, 14.81.

5-Dimethylamino-1,3-diphenylhydantoin (**3.24f**) The reaction mixture was cooled to 0 °C and $NaBH_4$ (20 mmol) was added. The mixture was slowly heated to reflux before cooled to 0 °C and quenched with water (20 mL), dropwise. The organic phase was diluted with diethyl ether (30 mL) and washed with water (2 x 40 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by column chromatography gave the product as an oil which was triturated with hexane to crystallize out the product **3.24f** as a white solid (0.75 g, 51%): mp 113 °C; ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 6 H), 5.22 (s, 1 H), 7.22-7.30 (m, 1 H), 7.36-7.53 (m, 7 H), 7.60 (d, J = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$): δ 38.96, 77.23, 122.55, 125.84, 126.29, 128.39, 129.10, 131.17, 136.23, 153.03, 168.59. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.12; H, 5.81; N, 14.23. Found: C, 69.16; H, 5.69; N, 14.33.

5-Ethyl-5-dimethylamino-1,3-diphenylhydantoin (**3.24g**) The reaction mixture was cooled to 0 °C and then quenched with EtMgBr (11 mmol) in diethyl ether. The mixture was allowed to warm to room temperature and stirred for 1 h before quenched with water (20 mL), dropwise. The mixture was filtered and the organic phase was diluted with diethyl ether (30 mL) and washed with water (2 x 40 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by column chromatography with ethyl acetate/hexane (1:1) as the eluent gave the product as an oil which was triturated with hexane to crystallize product **3.24g** as a white solid (0.90 g, 56%): mp 110-111 °C; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.4 Hz, 3 H), 1.85 (overlapping dq, J = 13.9, 7.4 Hz, 1 H), 2.37 (overlapping dq, J = 13.9, 7.2 Hz, 1 H), 2.58 (s, 6 H), 7.24-7.31 (m, 1 H), 7.35-7.53 (m, 7 H), 7.75 (d, J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$): δ 7.85, 24.99, 38.11, 84.68, 125.20, 126.27, 126.45, 128.23, 128.81, 128.99, 131.22, 135.21, 153.98, 170.98. Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.55; H, 6.55; N, 13.00. Found: C, 70.56, H, 6.56; N, 13.04.

Procedure for Compounds **3.27** and **3.28**.

A solution of *N,N*-dimethylbenzotriazolylmethyleneiminium (**3.1**) (1.06 g, 5 mmol), *trans*-dibenzoylethylene (**3.25**) (1.18 g, 5 mmol) and triethylamine (1.01 g, 10 mmol) in dry benzene (20 mL) was refluxed for 24 h. After diluted with diethyl ether (30 mL), the mixture was washed with 10% Na_2CO_3 (40 mL) and water (40 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by column chromatography gave **3.27** as an oil (0.22 g, 15%) and **3.28** as a solid (0.11 g, 6%).

2-Dimethylamino-3-benzoyl-5-phenylfuran (**3.27**): ^{1}H NMR ($CDCl_3$) δ 3.24 (s, 6 H), 6.71 (s, 1 H), 7.18 (t, *J* = 7.4 Hz, 1 H), 7.33 (t, *J* = 7.4 Hz, 2 H), 7.43-7.57 (m, 5 H), 7.85 (d, *J* = 6.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 40.25, 101.29, 109.21, 122.43, 126.38, 128.16, 128.59, 128.92, 130.15, 131.21, 140.63, 142.20, 162.15, 187.66. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.89; N, 4.81. Found: C, 77.98, H, 5.79; N, 4.79.

2-Phenyl-3-[benzotriazol-1-yl]-4-benzoylfuran (**3.28**): mp 175-177 °C; ^{1}H NMR ($CDCl_3$): δ 7.21-7.54 (m, 11 H), 7.76 (d, *J* = 7.2 Hz, 2 H), 8.07 (s, 1 H), 8.11 (d, *J* = 8.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$): δ 110.10, 116.79, 120.10, 124.20, 124.67, 125.39, 127.10, 128.37, 128.44, 128.75, 128.87, 129.64, 133.05, 134.50, 137.51, 145.59, 146.78, 151.16, 187.36. Anal. Calcd for $C_{23}H_{15}N_3O_2$: C, 75.59; H, 4.14; N, 11.51. Found: C, 75.56, H, 4.07; N, 11.53.

X-ray Crystallography

(This work was done by Mr. Chris M. Hartshorn and Dr. Peter J. Steel, Chemistry Department, University of Canterbury, Christchurch, New Zealand.) Intensity data were collected with a Nicolet P4s four-circle diffractometer by using monochromatized Mo Kα (λ = 0.71073 Å) radiation. The crystal used was a pale yellow block of dimensions 0.74 x 0.72 x 0.48 mm. Throughout data collections the intensities of the three standard reflections were monitored at regular intervals and the intensities were corrected for minor decay (< 9%). The intensities were also corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods using SHELXS90 [90ACSA467], and refined on F^2 by full-matrix least-squares procedures using SHELXL93 [93MI1]. All non-hydrogen atoms were refined with anisotropic displacement coefficients. Hydrogen atoms were included in calculated positions with isotropic displacement coefficients equal to 1.3 times the isotropic equivalent of their carrier carbons. The function minimized was $\Sigma w(F_o^2 - F_c^2)$, with $w = [\sigma^2(F_o^2) + 0.0742P^2]^{-1}$, where $P = [\max(F_o^2) + 2F_c^2]/3$. A final difference map showed no features greater or less than $0.27e^-/Å^3$. Final non-hydrogen atom coordinates, bond lengths and bond angles are listed in Tables 2 and 3. Tabulations of hydrogen atom coordinates, anisotropic thermal parameters, structure factors and equations of meanplanes are available from the author PJS.

Crystal data for **3.28** -115 °C : $C_{23}H_{15}N_3O_2$, Mr = 365.4, triclinic, space group P-1, a = 6.653(1), b = 11.667(2), c = 12.716(1) Å, α = 63.17(1), β = 80.21(1)°, γ = 82.12(1), U = 865.9(2) $Å^3$, F(000) = 380, Z = 2, D_c = 1.401 g cm^{-3}, μ(Mo-Kα) = 0.92 cm^{-1}, ω scans, 2 θ_{max} = 55°, 253 parameters, S = 0.95, wR2 = 0.115 for all 3831 data, R1 = 0.044 for 2775 data with $F_o > 4\sigma(F_o)$.

Table 3.2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2x10^3$)

atom	x	y	z	U_{eq}[a]
O1	3099(2)	8757(1)	5096(1)	28(1)
C2	4878(2)	8233(1)	4704(1)	25(1)
C3	5738(2)	9168(1)	3688(1)	24(1)
C4	4427(2)	10329(1)	3399(1)	24(1)
C5	2874(2)	10008(1)	4305(1)	27(1)
C21	5388(2)	6864(1)	5394(1)	26(1)
C22	3826(2)	6021(2)	5946(1)	31(1)
C23	4287(3)	4716(2)	6573(1)	35(1)
C24	6309(3)	4233(2)	6648(2)	37(1)
C25	7866(3)	5056(2)	6110(2)	36(1)
C26	7424(2)	6367(2)	5490(1)	32(1)
N31	7572(2)	8987(2)	3012(1)	24(1)
N32	9450(20	9026(1)	3302(1)	29(1)
N33	10864(2)	8804(1)	2554(1)	29(1)
C31	9919(2)	8627(1)	1759(1)	24(1)
C32	10735(2)	8367(1)	794(1)	29(1)
C33	9383(2)	8260(2)	155(1)	32(1)
C34	7239(2)	8416(2)	437(1)	31(1)
C35	6397(2)	8668(1)	1383(1)	27(1)
C36	7798(2)	8757(1)	2042(1)	22(1)
C40	4787(2)	11570(2)	2352(1)	26(1)
O4	6437(2)	11715(1)	1727(1)	41(1)
C41	3142(2)	12633(1)	2058(1)	26(1)
C42	3738(2)	13895(2)	1459(1)	31(1)
C43	2281(3)	14919(2)	1156(2)	36(1)
C44	210(3)	14700(2)	1425(2)	36(1)
C45	-383(2)	13455(2)	1992(2)	35(1)
C46	1060(2)	12423(2)	2311(1)_	29(1)

[a] equivalent isotropic U defined as one third of the trace of the orthogonal zed Uij tensor.

Table 3. Bond Lengths (Å) and angles (°) for **3.28**.

O1-C2	1.378(2)	O1-C5	1.353(2)	C2-C3	1.354(2)
C2-C21	1.457(2)	C3-N31	1.418(2)	C3-C4	1.437(2)
C4-C5	1.359(2)	C4-C40	1.474(2)	C21-C22	1.396(2)
C21-C26	1.400(2)	C22-C23	1.381(2)	C23-C24	1.386(2)
C24-C25	1.385(2)	C25-C26	1.375(2)	N31-N36	1.356(2)
N31-N32	1.373(2)	N32-N33	1.307(2)	N33-N31	1.378(2)
C31-C32	1.398(2)	C31-C36	1.401(2)	C32-C33	1.363(2)
C33-C34	1.418(2)	C34-C35	1.376(2)	C35-C36	1.397(2)
C40-O4	1.224(2)	C40-C41	1.491(2)	C41-C42	1.396(2)
C41-C46	1.397(2)	C42-C43	1.381(2)	C43-C44	1.392(2)
C44-C45	1.378(2)	C45-C46	1.382(2)		

C5-O1-C2	107.46(11)	C3-C2-O1	108.30(13)
C3-C2-C21	134.45(14)	O1-C2-C21	117.20(13)
C2-C3-N31	124.70(14)	C2-C3-C4	108.37(13)
N31-C3-C4	126.86(13)	C5-C4-C3	104.38(13)
C5-C4-C40	129.77(14)	C3-C4-C40	125.85(13)
O1-C5-C4	111.45(13)	C22-C21-C26	119.06(14)
C22-C21-C2	119.63(14)	C26-C21-C2	121.29(14)
C23-C22-C21	120.3(2)	C22-C23-C24	120.1(2)
C25-C24-C23	119.9(2)	C26-C25-C24	120.5(2)
C25-C26-C21	120.1(2)	C36-N31-N32	110.36(11)
C36-N31-C3	128.42(12)	N32-N31-C3	121.22(12)
N33-N32-N31	108.42(12)	N32-N33-C31	108.33(12)
N33-C31-C32	130.92(13)	N33-C31-C36	108.73(12)
C32-C31-C36	120.35(13)	C33-C32-C31	117.08(14)
C32-C33-C34	122.07(14)	C35-C34-C33	122.0(2)
C34-C35-C36	115.39(14)	N31-C36-C35	132.75(13)
N31-C36-C31	104.15(12)	C35-C36-C31	123.09(13)
O4-C40-C4	119.46(14)	O4-C40-C41	120.59(14)
C4-C40-C41	119.96(13)	C42-C41-C46	119.05(14)
C42-C41-C40	117.65(13)	C46-C41-C40	123.25(14)
C43-C42-C41	120.2(2)	C42-C43-C44	120.3(2)
C45-C44-C43	119.7(2)	C44-C45-C46	120.6(2)
C45-C46-C41	120.2(2)		

Figure 3.12 shows a perspective view and atom labeling of the X-ray crystal structure of **3.28**, which confirms the structure and substitution pattern in the furan ring. Tables 3.2 and 3.3 list atom coordinates and bonding geometries. Each of the aromatic ring systems is planar to within 0.01 Å, with the furan ring inclined to the meanplanes of the C2-phenyl, C3-benzotriazole, and C4-phenyl ring planes at angles of 34.7(1), 81.2(1) and 36.3(1) °, respectively. The mutually orthogonal orientation of the furan and benzotriazole rings results in an interesting packing of the molecules within the crystal lattice. The intramolecular bonding geometry shows no unusual features, and there are no intermolecular contacts between non-hydrogen atoms of less than 3.2 Å.

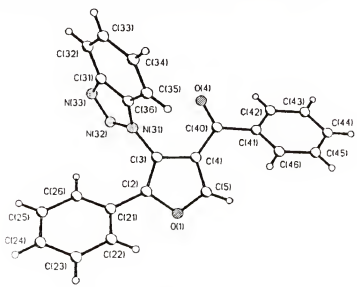


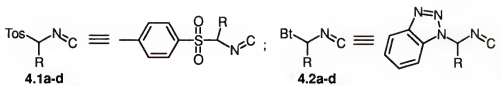
Figure 3.12

CHAPTER 4
SYNTHESIS OF IMIDAZLOLES AND PYRROLES USING BETMIC IN COMPARISON WITH TOSMIC

4.1 Introduction

p-Tolylsulfonylmethyl isocyanide (TosMIC, **4.1a**), which embodies the α-anion stabilizing effect of the tosyl and isocyano groups and the electrophilicity of the isocyano group (R = H, Figure 4.1), has become a versatile building block [80LHCS111] [74AG(E)789] [77AG(E)339] [93OPPI143]. α-Metallated TosMIC derivative **4.3** possesses a nucleophilic center, which may be added to polar multiple bonds, and an electrophilic center, the isocyanide group, which allows subsequent heterocyclization [93OPPI143] (Figure 4.2). This strategy has been applied to the synthesis of oxazoles and oxazolines [72TL2369] [77H77], imidazoles [77JOC1153], pyrroles [72TL5337] [90T7587] [91T4639] [92JOC2245], tosyl substituted thiazoles [82RTCP28], ketones [77TL4229] and α-hydroxy aldehydes from ketones [74TL167]. The TosMIC methodology has also found applications in the modification of steroids [84TL2581] [92RTCP469], synthesis of benzazole rings [86TL2173] [86JOC4131], and synthesis of porphyrins [88CL1891].

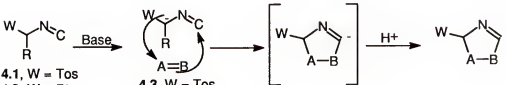
Benzotriazol-1-yl-methyl isocyanide (BetMIC, **4.2a**, Figure 4.1) exhibits properties which are qualitatively similar to (Figure 4.2), but differ quantitatively from those of TosMIC **4.1a** (R = H). For example, BetMIC **4.2a** has been used to synthesize α-hydroxy aldehydes (without employing thallium (I) ethoxide which is needed with TosMIC **4.1a**)



4.1a-d **4.2a-d**

4.1a, **4.2a**, R = H;
4.1b, **4.2b**, R = Me;
4.1c, **4.2c**, R = $PhCH_2$;
4.1d, **4.2d**, R = Ph.

Figure 4.1



4.1, W = Tos
4.2, W = Bt

4.3, W = Tos
4.4, W = Bt

Figure 4.2

and oxazoles [89TL6657] **4.10** (Figure 4.3). Theoretically, a tosyl group stabilizes the α-anion *via* both inductive effect and mesomeric effect while a Bt group stabilizes the α-anion only by inductive effect. In fact, TosMIC **4.1a** can be dilithiated with *n*-BuLi [80TL3723], monodeprotonated [72TL2369] [77H77] [77JOC1153] [72TL5337] (at least partially to induce nucleophilic attack) by NaH, *t*-BuOK, K_2CO_3, RNH_2, *etc.* In contrast, *t*-BuOK is the only base, among a variety of bases studied (see the results below), that has been used successfully to induce nucleophilic attack of BetMIC **4.2a**. Conceivably, since the α-anionic BetMIC derivative **4.4** is less stabilized than that of TosMIC derivative **4.3**, anion **4.4** should be more reactive than anion **4.3**, which could be advantageous in certain circumstances. This idea was inspired by literature studies which showed that TosMIC derivative **4.1** generally gave high yields of oxazoles **4.10** in reacting with aldehydes **4.5** [72TL2369] [77H77] (Figure 4.3), while in preparing imidazoles **4.16** (Figure 4.4) and pyrroles **4.22** (Figure 4.5) by reacting with carbon-nitrogen **4.11** and carbon-carbon double

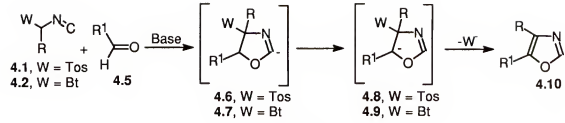
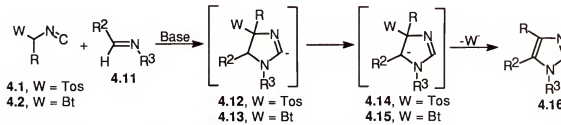
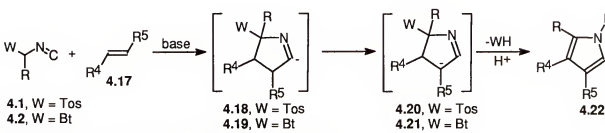


Figure 4.3



For designation of R, R2, R3, see Figure 4.1 and Table 4.1

Figure 4.4



For designation of R, R4, R5, see Figure 4.1 and Table 4.2

Figure 4.5

bonds **4.17** which are generally less reactive than aldehydes **4.5**, **4.1** in some cases gave low yields [77H77] [77JOC1153] [72TL5337].

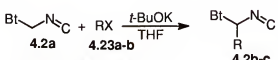
This chapter focuses upon comparison of the utilities of TosMIC derivatives **4.1** and BetMIC derivatives **4.2** in the preparation of imidazoles **4.16a-h** (Table 4.1) and pyrroles **4.22a-i** (Table 4.2). The strategy used for this comparative study involved the selection of reactions from the literatures for which TosMIC derivatives **4.1** reportedly gave little or

no product. The same reactions were attempted with BetMIC derivatives **4.2** to determine if any improvement in the yields of could be obtained.

4.2 Results and Discussions

Preparation of BetMIC Derivatives **4.2a-d**

Compound **4.2a** and **4.2d** (Figure 4.1) were prepared according to the literature method [90JCS(P1)1847]. The preparation of α-alkyl substituted derivatives of BetMIC **4.2b,c** is shown in Figure 4.6. Among a variety of bases tested (BuLi, LDA, NaH, *t*-BuOK, DBU, KOH, lithiated fluorene, etc), *t*-BuOK gave the best results to generate the BetMIC anion **4.4a** (R = H, Figure 4.2) which upon reacting with alkyl halides **4.23a,b** gave the alkylated BetMIC **4.2b,c** (Figure 4.6). Dialkylation was found as a side-reaction. Other bases either resulted in decomposition of BetMIC **4.2a** or were not basic enough to deprotonate BetMIC **4.2a**.



4.2a **4.23a-b** **4.2b-c**

4.23a: R = Me, X = I;
4.23b: R = $PhCH_2$, X = Cl;
4.2b: R = Me;
4.2c: R = $PhCH_2$.

Figure 4.6

Preparation of Imidazoles **4.16a-h**

α-Metallated isocyanides add to imines to form imidazolines [93OPPI143]. When a methyl isocyanide with a good leaving group (such as tosyl in TosMIC **4.1**) is used, imidazoles **4.16** are often obtained (Figure 4.4). The bases used in these reactions with TosMIC derivatives **4.1** were potassium carbonate, sodium hydride, *t*-butylamine and cyclohexylamine [77H77] [77JOC1153].

As expected, BetMIC (derivatives) **4.2a-d** reacted with aldimines **4.11** in a similar fashion to TosMIC derivatives **4.1a-d** to form imidazoles **4.16b,c,e-h** (Figure 4.4 and Table 4.1) under basic conditions. In this case, the Bt group stabilized the anion formed in the first step and was spontaneously eliminated from the intermediate imidazoline anion **4.15**. The reactions were attempted in a variety of bases and solvents. BetMIC (derivatives) **4.2a-d** were found to decompose in the presence of strong bases such as LDA, *n*-BuLi and sodium hydride. The most effective conditions for all of these reactions was found to be *t*-BuOK in DMSO or THF.

Table 4.1 shows a selection of the reactions reported in the literatures [77H77] [77JOC1153] which used TosMIC **4.1a-d**. In the case of the reaction of diaryl aldimines **4.11**, the best results were obtained when an electron withdrawing group is present on at least one of the aryl substituents R^2, R^3 (entries 1 and 4) [77H77] [77JOC1153]. Reactions that were reported to give low yields with TosMIC derivatives **4.1a-d** have now been attempted with BetMIC derivatives **4.2a-d** and these results are also shown in Table 4.1. For diaryl aldimines without electron withdrawing groups on R^2 and R^3, much better yields were obtained with BetMIC derivatives **4.2a-d** than with TosMIC derivatives **4.1a-d** (entries 2, 3, 5 and 8). In the case of *N*-alkyl aldimines **4.11** for which TosMIC (derivatives) **4.1a,c** had produced low yields, BetMIC (derivatives) **4.2a,c** also gave low yields (entries 6 and 7).

Table 4.1. Synthesis of Imidazoles **4.16a-h**: Literature Using TosMIC **4.1a-d** Compared with the New Route Using BetMIC **4.2a-d** (Figure 4.4).

entry	R	R^2	R^3	TosMIC	BetMIC	
				4.16, Yield (%)	Method[c]	Yield (%)
1	Me	Ph	p-$NO_2C_6H_4$	**a**, 75 [a,b]	-	-
2	Ph	Ph	Ph	**b**, 0 [b]	A	23
3	Me	Ph	Ph	**c**, 0 [a]	A	67
4	$PhCH_2$	p-ClC_6H_4	Ph	**d**, 68 [a]	-	-
5	$PhCH_2$	p-$MeOC_6H_4$	Ph	**e**, 0 [a]	B	73
6	H	Ph	Me	**f**, 10 [b]	A	10
7	$PhCH_2$	Ph	Me	**g**, 0 [a]	A	0
8	H	Ph	Ph	**h**, 56 [b]	B	85

[a]: [77H77]; [b]: [77JOC1153]; [c]: see the Experimental section.

Preparation of Pyrroles **4.22a-i**.

TosMIC (derivatives) **4.1a,b** react with electron deficient alkenes **4.17** to form pyrroles **4.22a-i** (Figure 4.5), in an analogous fashion to its reaction with aldimines **4.11**, to form imidazoles **4.17a-h**. BetMIC (derivatives) **4.2a,b** undergo a similar reaction with electron deficient alkenes **4.17** (Figure 4.5).

Selected literature results of reactions of TosMIC (derivatives) **4.1a,b** with electron-deficient alkenes **4.17** [77H77] [72TL5337] and newly undertaken comparative reactions of BetMIC (derivatives) **4.2a,b** are shown in Table 4.2. All the acrylonitriles **4.17** (entries 7-9) and the terminally unsubstituted unsaturated esters and ketones **4.17** (entries 2, 5 and 6) gave poor yields of pyrrole when reacted with TosMIC (derivatives) **4.1a-b**. The use of BetMIC **4.2a** dramatically improved the yields of 3-cyanopyrroles **4.22g-i** from acrylonitrile derivatives **4.17** (entries 7-9) and somewhat improved the yields of 4-unsubstituted 3-methoxycarbonylpyrroles **22e,f** from methyl acrylate **4.17** (entries 5 and 6). However for entries 2 and 3 TosMIC **4.1a** gave better results than BetMIC **4.2a**.

Table 4.2. Synthesis of Pyrroles **4.22a-i**: Literature Using TosMIC **4.1a,b** Compared with Using BetMIC **4.2a,b** (Figure 4.5).

entry	R	R^4	R^5	TosMIC	BetMIC	
				4.22, yield (%)	method[c]	yield (%)
1	H	Ph	COMe	**a**, 70 [a]	-	-
2	H	H	COMe	**b**, 15 [a]	A	0
3	H	Ph	COOMe	**c**, 70 [a]	A	40
4	H	Me	COOMe	**d**, 64 [a]	-	-
5	H	H	COOMe	**e**, 33 [a]	A	45
6	Me	H	COOMe	**f**, 0 [b]	B	30
7	H	Ph	CN	**g**, 35 [a]	A	81
8	H	Me	CN	**h**, 50 [a]	A	92
9	H	H	CN	**i**, 10 [a]	A	63

[a]: [77H77]; [b]: [72TL5337]; [c]: see the Experimental section.

4.4 Experimental

General

Aldimines **4.11** were either from commercial sources or prepared by refluxing equimolar of the corresponding aldehydes and amine (anilines) in toluene with a Dean-Starke to remove the water generated. THF was distilled prior to use from a purple solution resulting from benzophenone and sodium. DMSO was dried over molecular 4 Å sieves. Column chromatography was carried out on MCB silica gel (230-400 mesh). Other chemicals were used as obtained from commercial sources. Reactions were routinely carried out under dry nitrogen atmosphere with magnetic stirring.

Melting points were determined on a hot stage apparatus without correction. NMR spectra were obtained with a Varian Gemini-300 spectrometer at 75 MHz for ^{13}C and 300 MHz for ^{1}H. Both ^{13}C and ^{1}H NMR spectra were obtained in chloroform-*d*, chemical shift

values are reported as δ downfield from TMS as an internal standard. Elemental analyses was performed within the department on a Carlo Erba-1106 instrument.

Procedure for Preparation of BetMIC Derivatives **4.2b,c**

t-BuOK (6.0 mmol) in THF (10 mL) was added dropwise to a stirred mixture of BetMIC **4.2a** (0.79g, 5.0 mmol) and methyl iodide (0.71g, 5.0 mmol) or benzyl chloride (0.63g, 5 mmol), in THF (20 mL) at -78 °C. The reaction mixture was allowed to warm to room temperature, water was added, the solution extracted with ether, the ether extract dried ($MgSO_4$) and evaporated to dryness. Column chromatography with ethyl acetate/hexane (1:3) as the eluent gave, as oils, 1-(benzotriazol-1-yl)ethyl isocyanide (**4.2b**) or 1-(benzotriazol-1-yl)-2-phenylethyl isocyanide (**4.2c**).

1-(Benzotriazol-1-yl)ethyl isocyanide (**4.2b**) (0.46 g, 53%): ^{1}H NMR δ 2.23 (d, J = 6.8 Hz, 3 H), 6.57 (q, J = 6.8 Hz, 1 H), 7.45 (t, J = 7.2 Hz, 1 H), 7.59 (t, J = 7.3 Hz, 1 H), 7.73 (d, J = 8.4 Hz, 1 H), 8.11 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 21.8, 62.5, 109.6, 120.7, 124.9, 128.6, 130.9, 146.6, 162.1. Anal. Calcd for $C_9H_8N_4$: C, 62.79; H, 4.65; N, 32.56. Found: C, 63.11; H, 4.80; N, 32.66.

1-(Benzotriazol-1-yl)-2-phenylethyl isocyanide (**4.2c**) (0.62 g, 50%): ^{1}H NMR δ 3.78 (d, J = 7.1 Hz, 2 H), 6.55 (t, J = 7.1 Hz, 1 H), 7.10-7.70 (m, 8 H), 8.12 (d, J = 8.4 Hz, 1 H).

Procedures for Synthesis of Imidazoles **4.16b,c,e-h** with BetMIC Derivatives **4.2a-d**

Method A: To a stirred solution of BetMIC derivative **4.2a-d** (5.0 mmol) and aldimine **4.11** (5.0 mmol) in THF (25 mL) at 0 °C was added dropwise a solution of potassium *tert*-butoxide (1.12g, 10.0 mmol) in THF (15 mL). The reaction mixture was

heated to reflux, cooled, evaporated to dryness and the residue extracted with ether (2 x 50 mL). The extracts were evaporated to dryness and the residue subjected to column chromatography with ethyl acetate/hexane (1:1) as eluent to give products **4.16b,c,f,g**.

Method B: This procedure is similar to the above Method A except that DMSO (rather than THF) was used as the solvent, addition took place at room temperature and that after heating to 75 °C, the mixture was cooled, diluted with water and extracted with ether (3 x 40 mL). The ether extracts were washed with water and dried with $MgSO_4$, evaporated to dryness and the residue subjected to column chromatography with ethyl acetate/hexane (1:1) as eluent to give products **4.16e,h**.

1,4,5-Triphenylimidazole (**4.16b**) (0.34 g, 23%): mp 268-270 °C, lit. mp 270-272 °C [86BCSB655]; ^{1}H NMR δ 7.09-7.34 (m, 13 H), 7.52-7.56 (m, 2 H), 7.78 (s, 1 H); ^{13}C NMR δ 125.8, 126.7, 127.3, 127.9, 128.10, 128.17, 128,6, 128.7, 129.2, 130.2, 130.8, 134.5, 136.5, 138.0, 139.0.

1,5-Diphenyl-4-methylimidazole (**4.16c**) (0.78 g, 67%): mp 97-98 °C; ^{1}H NMR δ 2.38 (s, 3 H), 7.10-7.14 (m, 4 H), 7.20-7.40 (m, 6 H), 7.67 (s, 1 H); ^{13}C NMR δ 13.6, 125.2, 127.1, 127.5, 128.2, 129.2, 129.7, 130.0, 136.6, 136.9 (two carbons unresolved). Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.05; H, 5.98; N, 11.96. Found: C, 81.82; H, 6.05; N, 12.18.

1-Phenyl-4-benzyl-5-(4-methoxyphenyl)imidazole (**4.16e**) (1.24 g, 73%): oil; ^{1}H NMR δ 3.79 (s, 3 H), 3.97 (s, 2 H), 6.81 (d, J = 8.8 Hz, 2 H), 7.02 (d, J = 8.8 Hz, 2 H), 7.07-7.40 (m, 10 H), 7.67 (s, 1 H); ^{13}C NMR δ 33.7, 55.2, 113.8, 122.0, 125.3, 125.9, 127.5, 128.4, 128.7, 129.2, 131.3, 136.7, 136.9, 139.0, 140.9, 159.0 (one carbon unresolved). Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.18; H, 5.88; N, 8.24. Found: C, 80.80; H, 6.02; N, 8.50.

1-Methyl-5-phenylimidazole (**4.16f**) (79 mg, 10%): mp 94-95 °C, lit. mp 94-95 °C [77JOC1153]; ^{1}H NMR δ 3.67 (s, 3 H), 7.12 (s, 1 H), 7.30-7.50 (m, 5 H), 7.52 (s, 1 H); ^{13}C NMR δ 32.4, 127.8, 128.1, 128.4, 128.7, 129.8, 133.4, 139.0.

1,5-Diphenylimidazole (**4.16h**) (0.94 g, 85%): mp 130-131 °C, lit. mp 130-131 °C [77JOC1153]; ^{1}H NMR δ 7.13-7.29 (m, 8 H), 7.38-7.41 (m, 3 H), 7.71 (s, 1 H); ^{13}C NMR δ 125.7, 127.5, 128.1, 128.2, 128.4, 129.0, 129.45, 129.52, 133.1, 136.8, 138.9.

Procedures for Synthesis of Pyrroles **4.22b,c,e-i** with BetMIC **4.2a,b**

Method A: To a stirred solution of (alkylated) BetMIC **4.2a,b** (5.0 mmol) and alkene **4.17** (5.0 mmol) in THF (25 mL) at 0 °C was added a solution of *t*-BuOK (1.12 g, 10 mmol) in THF (15 mL). The reaction mixture was heated to reflux, cooled, water was added, the solution brought to a pH of 5 with HCl (10%) and the mixture extracted with ether. The dried extracts ($MgSO_4$) were evaporated to dryness and the residue subjected to column chromatography with ethyl acetate/hexane (1:1) as eluent to give products **4.22b-c,e,g-i**.

Method B: This procedure is similar to the above method except that a solution of *t*-BuOK (1.12 g, 10 mmol) in THF (15 mL) was added to a solution of (alkylated) BetMIC (5.0 mmol) in THF (15 mL) at -78 °C. The electrophile was then added dropwise, the mixture was warmed slowly to room temperature, heated to reflux and the procedure continued as above to give **4.22f**.

3-Phenyl-4-(methylcarboxyl)pyrrole (**4.22c**) (0.40 g, 40%): mp 181-183 °C, lit.mp 182-183 °C [72TL5337]; ^{1}H NMR δ 3.76 (s, 3 H), 6.80 (t, J = 2.4 Hz, 1 H), 7.29-7.53 (m, 6 H), 8.50 (br s, 1 H); ^{13}C NMR δ 50.6, 118.4, 125.35, 125.44, 126.2, 127.6, 129.1, 129.2, 134.9, 165.3.

3-(Methylcarboxyl)pyrrole (**4.22e**) (0.28 g, 45%): mp 86-88 °C, lit. mp 86-87 °C [72TL5337]; ^{1}H NMR δ 3.83 (s, 3 H), 6.60-6.70 (m, 1 H), 6.75-6.78 (m, 1 H), 7.40-7.45 (m, 1 H), 8.80 (br s, 1 H); ^{13}C NMR δ 51.1; 109.8, 116.3, 118.8, 123.5, 165.6.

2-Methyl-4-(methylcarboxyl)pyrrole (**4.22f**) (0.21 g, 30%): mp 114-115 °C, lit. mp 117-118 °C [86JACS6739]; ^{1}H NMR δ 2.26 (s, 3 H), 3.80 (s, 3 H), 6.30 (s, 1 H), 7.27-7.29 (m, 1 H), 8.40 (br s, 1 H); ^{13}C NMR δ 12.8, 51.0, 107.1, 116.3, 122.4, 128.8, 165.7.

3-Cyano-4-phenylpyrrole (**4.22g**) (0.68 g, 81%): mp 126-127 °C, lit. mp 128-129 °C [72TL5337]; ^{1}H NMR δ 6.99 (t, J = 2.4 Hz, 1 H), 7.26-7.44 (m, 4 H), 7.60-7.80 (m, 2 H), 8.90 (br s, 1 H); ^{13}C NMR δ 91.7, 116.5, 117.0, 126.6, 127.2, 127.3, 128.5, 128.9, 132.8.

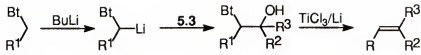
3-Cyano-4-methylpyrrole (**4.22h**) (0.49 g, 92%): mp 114-116 °C, lit. mp 114-117 °C [72TL5337]; ^{1}H NMR δ 2.19 (s, 3 H), 6.57 (s, 1 H), 7.20 (s, 1 H), 8.50 (br s, 1 H); ^{13}C NMR δ 10.3, 94.0, 116.7, 122.1, 125.3 (one carbon unresolved).

3-Cyanopyrrole (**4.22i**) (0.29 g, 63%): mp 54-55 °C, lit. mp 53-55 °C [72TL5337]; ^{1}H NMR δ 6.48-6.51 (m, 1 H), 6.81-6.84 (m, 1 H), 7.31-7.34 (m, 1 H), 8.90 (br s, 1 H); ^{13}C NMR δ 92.9, 111.6, 116.9, 119.2, 125.7.

CHAPTER 5
BENZOTRIAZOLE-MEDIATED STEREOSELECTIVE OLEFINATION OF CARBOXYLIC ESTERS AND ITS APPLICATION TO α-AMINO ACID ESTERS

5.1 Introduction

Constructive olefination of carbonyl compounds is one of the most important transformations in organic synthesis. Wittig, Peterson and Julia reactions are the three mostly used procedures [95MI589, 719] [91MI729]. Low valent titanium induced coupling of carbonyl compounds has received wide applications in intramolecular cyclizations [89CR1513] [96AG2443], while its intermolecular version generally suffers from statistical cross-overs. Recently, Horikawa *et al* reported unsymmetrical intermolecular coupling between carbonyl compounds and dithioacetals with low valent titanium, but the products are generally a mixture of *cis*- and *trans*-isomers with little diastereoselectivity [97JACS1127]. A recently published procedure of low valent titanium effected dehydroxybenzotriazolylation (Figure5.1) [97JOC238] shows diastereoselectivity for *trans*-isomers and constitutes an alternative to the Julia reaction. The α-anion-stabilizing effect of the Bt group enhances the deprotonation of the benzylic and allylic substrates **5.1** to form the anion **5.2**, which undergoes nucleophilic attack to connect to carbonyl compounds **5.3** to form β-hydroxy benzotriazole derivatives **5.4** (Figure 5.1). Although so far the work has been confined to benzylic and allylic substrates, it is just with these substrates that Wittig reaction generally lacks selectivity [95MI719] [91MI729]. The significance of this method



5.1 5.2 5.4 5.5

Bt = 1-benzotriazolyl; R^1 = aryl, alkenyl;
5.3 = aldehydes or ketones, R^2COR^3.

Figure 5.1

lies in reductive dehydroxybenzotriazolylation of **5.4** under low-valent titanium conditions leading to *trans*-olefins.

While most olefination methods were developed to construct double bonds from aldehydes and ketones, some have been applied to carboxylic esters [95MI589, 719] [91MI729]. Carboxylic esters have been used in Horner-Wittig reaction to obtain selectivity (*via* selective reduction) for *threo*- diastereomers of the β-hydroxy phosphine oxide which upon elimination led to *trans*-products with stereospecificity [85JCS(P1)2307]. The Julia reaction has been applied to construct double bonds from carboxylic esters in some natural product syntheses [91MI729] [86JACS284]. However, to the best of our knowledge, little effort (if any) has been made to systematically study the olefination of carboxylic esters as a synthetic methodology. On the other hand, carboxylic esters are a very important functional group in organic chemistry and there are many cases in organic synthesis where as starting building blocks, carboxylic esters are much more readily available than the corresponding aldehydes. For example, the naturally occurring chiral α-amino acids can be easily converted to esters which are commercially cheap. In today's era of asymmetric synthesis, it is of great interest to explore these readily available and enantiomerically pure compounds as building blocks and/or to introduce chiral centers. An olefination of such type of compounds would lead to allylamines which are of great synthetic and biological importance [87AG320] [87JOC678] [89JOC3292] [91AJC627] [91JOC1027] [93HCA2602]. However, so far the synthetic transformations of the carbonyl groups in these α-amino acids have been mainly conducted through conversion into *N*-protected α-amino aldehydes,

including olefination *via* Wittig-type reactions which suffers from lack of general control of diastereoselectivity in the formation of the double bond and racemization of the chiral center [89CR149] [87JOC1487]. *N*-Protected α-amino aldehydes are known for their relative instability both chemically and configurationally [89CR149]. Although efforts have been made to improve their stability, it still takes a lengthy procedure to prepare them from corresponding acids *via* esters or active amides [89CR149] [87JACS236].

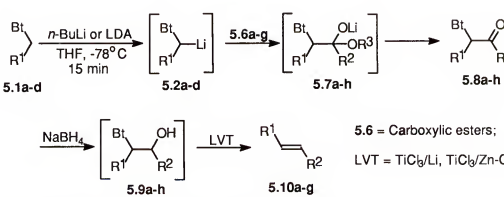
This chapter reports the elaboration of procedures as shown in Figure 5.2 and Figure 5.4 that effect diastereoselective olefination of carboxylic esters for *trans*-isomers. This comprises the preparation of α-(benzotriazol-1-yl) ketones **5.8a-i** from benzylic or allylic benzotriazole derivatives **5.1a-e** and carboxylic esters **5.6a-h**, subsequent reduction of **5.8a-i**, and finally low-valent titanium-promoted dehydroxybenzotriazolylation leading to alkenes **5.10a-h**. The stability of α-benzotriazol-1-yl ketones **5.8a-h** of benzylic substrates makes it convenient to investigate the procedure stepwise (Figure 5.2). A simple procedure without isolation of the intermediate **5.8i** (Figure 5.4) was developed to fit allylic substrate **5.1e**. This method has also been successfully applied to *N*-protected α-amino acid esters **5.14a-c** and **5.20** to synthesize allylamines **5.18a-e** and **5.25** (Figures 5.6 and 5.7). Compared with other methods of synthesizing chiral allyl amines (asymmetric allylic amination [89JACS6301] [91JACS3526], modification of enantiomerically pure α-amino aldehydes [87JOC1487] [94S31], asymmetric addition to alkynes [91JACS2321], and asymmetric nucleophilic addition to carbon-nitrogen double bonds [93HCA402] [93TA1603] [94JACS8797] [95HCA970] [96TA1887]), this constructive method constitutes a novel route featuring cheap starting materials and reagents, simple experimental performances, satisfactory overall yields, general preference for *trans*-olefinations and virtually full retention of the configurations of the chiral centers.

5.2 Results and Discussions

Preparation of the Starting Materials **5.1a-g**

1-Benzyl- and 1-allylbenzotriazoles **5.1** were readily prepared either by refluxing arylmethyl halides with benzotriazole in toluene (for compounds **5.1a,b,** Table 5.1) [94S597] [97JOC721] or by reacting the corresponding halides with benzotriazole in the presence of sodium hydroxide (for compound **5.1c**, **5.1e** and **5.1g**, Tables 5.1 and 5.2) [97JOC238] [56JCS1076] [95JA12015]. 1-[4-(*N*,*N*-Dimethylamino)]benzyl-benzotriazole (**5.1d**) (Table 5.1) was obtained from the reaction of 1-hydroxymethylbenzotriazole with *N*,*N*-dimethylaniline under acidic condition [90S341]. 2-(Benzotriazol-1-yl)methyl-4-(*t*-butyl)furan (**5.1f**) (Table 5.2) was prepared by a ring construction method previously reported [95JOC638].

All of these methods potentially give both the 1- and 2-benzotriazole isomers of the products. So far only the 1-Bt isomers **5.1a-g** have been used for the convenience of study. There has been evidence that 2-Bt isomers gave almost identical results (Dr. Li's work in other projects).



For designation of individual compounds, see Table 5.1

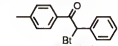
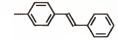
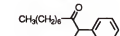
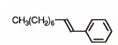
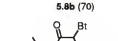
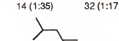
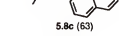
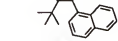
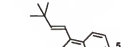
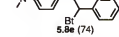
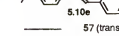
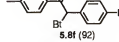
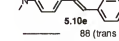
Figure 5.2

Preparation of α-Benzotriazol-1-yl Ketones **5.8a-h**

Compounds **5.8a-h** can be prepared by reacting **5.2a-d** with esters **5.6a-h** in an addition-elimination mode (Figure 5.2). The results were summarized in Table 5.1.

The yields of **5.8a-h** in Table 5.1 can be explained by conceivable side-reactions: i). the reaction between the lithiated starting material **5.2a-d** and the product **5.8a-h**: proton exchange and double addition; ii). the proton exchange between the lithiated starting materials **5.2a-d** and the esters **5.6** if they contain an α-H. The second side-reaction probably affected the yields of **5.8b,c,h** in Table 5.1. Whether the first side-reaction comes into effect depends on the relative stability of the semiacetal intermediates **5.7a-h** (Figure 5.2). Generally at low temperature, the semiacetals **5.7** were relatively stable and decomposed to corresponding products **5.8** rather slowly compared with the addition step. This accounts for the high yields of **5.8a**, **5.8f** and **5.8g**. For entry 4, because of steric hindrance the reaction had to proceed at elevated temperature and hence the ketone **5.8d** was the major product before quenched with water. Therefore proton exchange took place and almost half of the starting material was recovered. However, this problem was solved by using two equivalents of LDA as shown in entry 5 of Table 5.1. For entry 6, the semiacetal intermediate **5.7e** was less stable because of the presence of *para*-dimethylamino group and decomposed relatively faster to the ketone **5.8e**. In this case, both the starting material **5.1c** (because of proton exchange of **5.2c** with the product ketone **5.8e**) and the double addition product were found in the reaction mixture after quenching. Hence, the relative stability of the semiacetal intermediates **5.7** plays an important role in preventing the side reactions between the product ketones **5.8** and the lithiated starting material **5.2**.

Table 5.1 Preparation of α-Bt Ketones **5.8a-h** and Olefins **5.10a-g** (Figure 5.2)

entry	Bt-deriv. **5.1**	ester **5.6**	base	temperature (°C)	ketones **5.8** yield (%)	**5.10** yield (%) and selectivity [a] (*cis:trans*) $TiCl_3/Li$	$TiCl_3/Zn$-Cu
1	 **5.1a**	 **5.6a**	BuLi (1eq)	-78	 **5.8a** (96)	 **10a** 63 (1:28.5)	———
2	**5.1a**	 **5.6b**	BuLi (1eq)	-78	 **5.8b** (70)	 **5.10b** 14 (1:35)	32 (1:17.8)
3	 **5.1b**	**5.6c**	BuLi (1eq)	-78	 **5.8c** (63)	 **5.10c** 20 (1:23.8)	64 (1:17.2)
4	**5.1b**	 **5.6d**	BuLi (1eq)	-78 to 60	 **5.8d** (51)	 **5.10d**	
5	**5.1b**	 **5.6d**	LDA (2eq)	-78 to 60	**5.8d** (90)	70 (trans only)	77 (trans- only)
6	 **5.1c**	**5.6e**	BuLi (1eq)	-78	 **5.8e** (74)	 **5.10e** ———	57 (trans only)
7	 **5.1d**	 **5.6a**	BuLi (1eq)	-78	 **5.8f** (92)	 **5.10e** ———	88 (trans only)
8	**5.1c**	 **5.6f**	BuLi (1eq)	-78	 **5.8g** (95)	 **5.10f** ———	76 (1:19.2)
9	**5.1c**	 **5.6g**	BuLi (1eq)	-78 to -40	 **5.8h**[b] (72)	 **5.10g** ———	33 (1:3.4)

[a]: Overall yields starting from **5.8**; selectivity ratioes determined by ^1H NMR; isomers characterized by coupling constants and chemical shifts; [b]: two diastereomers without separation.

Reduction of α-Benzotriazol-1-yl Ketones **5.8a-h**

The α-benzotriazol-1-yl ketone **5.8a** (Table 5.1, entry 1) was studied for reduction under different conditions. With $LiAlH_4$ or $NaBH_4$ in an aprotic solvent (THF or DME), **5.8a** could not be quantitatively converted to **5.9a** (Figure 5.2) and the reaction mixture was

subject to decomposition. With $NaBH_4$ in ethanol at elevated temperature the reduction is quantitative and safe for all substrates **5.8a-h** attempted. According to ^1H NMR, the conversions were quantitative and the isolated yields of **5.9a-h** were about 95% as a mixture of diastereomers. The ratio between the diastereomers varied among different substrates but no high preference and no obvious pattern has been found. The diastereomers **5.9a-h** were not separated but were put directly to the olefination step.

An explanation for the above results is that part of the α-Bt ketone **5.8a** was irreversibly deprotonated in aprotic solvents to form the anionic enolate which was not reducible; however, in ethanol, the enolate anion can equilibrate with the solvent back to the reducible ketone form.

Dehydroxybenzotriazolylation with Low Valent Titanium

It has been shown [97JOC238] that the low-valent titanium reagent, generated from the reduction of $TiCl_3$ with lithium in THF or DME effectively promoted dehydroxy-benzotriazolylation from *N*-(β-hydroxyalkyl)benzotriazoles **5.4** (Figure 5.1) to form double bonds with the *trans*-isomers predominating. In the present work, the reagent ($TiCl_3$/Li) was used and as expected, treatment of the corresponding intermediates **5.9a-d** with $TiCl_3$/Li in DME under reflux gave the desired alkenes **5.10a-d** (Figure 5.2 and Table 5.1). However, the yields of **5.10b-c** by this procedure were low, although the *trans*-selectivities were excellent. It is assumed that the low yields were probably due to the poor reproducibility of $TiCl_3$/Li system as reported by McMurry [89CR1513]. Therefore, the more reproducible reagent $TiCl_3$/Zu-Cu, reported by McMurry and his co-workers [78JOC3255], was employed and this gave products **5.10a-h** in moderate to good yields. As shown in Table 5.1, the yields of **5.10b-d** were all improved considerably, however, it has to be noted that selectivities were slightly lower with $TiCl_3$/Zn-Cu than with $TiCl_3$/Li.

When the hydroxy group of **5.9** (Figure 5.2) was activated, it was found dehydration tended to be competitive under the reaction conditions, as is the case with entry 6 (Table 5.1), where dehydration products as a mixture of *cis*- and *trans*-isomers were also isolated. Similar results have been found in other research projects in the group.

It is tentatively assumed that the dehydroxybenzotriazolylations follow the similar mechanism to that of the McMurry coupling [89CR1513] as shown in Figure 5.3. The diastereomeric intermediates **5.9** were treated with low valent titanium to undergo sequential reductive cleavages to form **5.A** and radicals **5.B**. The radical intermediates **5.B** may then rotate to the thermodynamically favored configuration, followed by anti-elimination of the benzotriazolyl group to form *trans*-alkenes **5.10**. This proposed mechanism explains the *trans*-alkene predomination and is supported by our experimental results and literature evidence [78JOC3255] [89CR1513]. Based on this mechanism, the diastereoselectivity of the double bond formation depends on the rate with which the Bt group is cleaved: the more slowly it is cleaved, the more time the radical intermediate is allowed to rotate to assume the thermodynamically favoured configuration, the higher selectivity for *trans*-isomers. Since Zinc cation, generated from the reaction of $TiCl_3$ with Zn-Cu couple, can assist benzotriazolyl group to leave [94S445], higher yields and lower selectivities were obtained as compared with $TiCl_3$/Li in the cases of **5.10b-c**.

Actually, it was based on such a hypothesis that entries 6 and 7 (Table 5.1) were conducted: although both led to the same product **5.10e**, in the case of entry 6 where the hydroxy group is activated, it was expected to give lower yields but higher selectivity; in the case of entry 7 where the Bt group is activated, higher yield but lower selectivity. It turned out entry 7 does give a substantially higher yield, but because of the detecting limits of the methods available, no conclusion about the selectivity can be reached. On the other hand, this shows that although conceptually (based on the hypothesis) higher yield is concomitant with lower selectivity, it is posible to obtain a high yield together with a high selectivity.

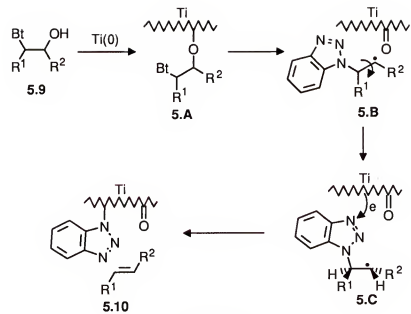


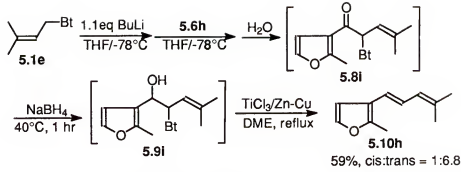
Figure 5.3

Allylic Substrate **5.1e**

For allylic substrate **5.1e**, it was found that the corresponding α-Bt ketones **5.8i** could be similarly prepared but were subjected to slow decomposition. Hence, **5.8i** was reduced *in situ* to avoid decomposition followed by dehydroxybenzotriazolylation to give **5.10h** in an overall 59% yield (Figure 5.4). Compared with the stepwise procedure in Figure 5.2, this procedure is more convenient and minimizes the loss of intermediates **8** and **9** caused by decomposition and isolation.

One-pot Approach from α-Benzotriazolyl Ketones **5.8**

It was anticipated that the transformation from **5.8** to **5.10** could be performed in one-pot by using $LiAlH_4$ to reduce ketones **5.8** and then to reduce $TiCl_3$ to generate the low-valent titanium. But it turned out that the reductive elimination of the Bt group dominated as shown in Figure 5.5.



5.6h = methyl 2-methyl-3-furancarboxylate

Figure 5.4

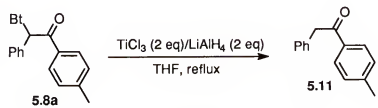
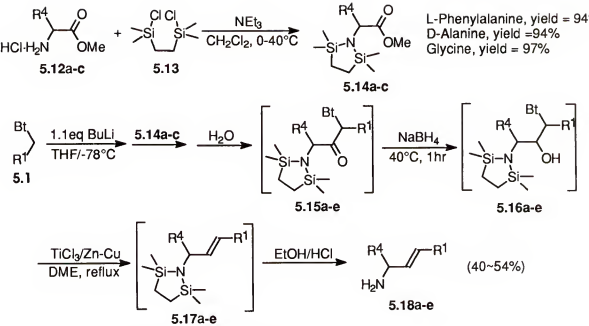


Figure 5.5

Primary α-Amino Acid Methyl Ester Hydrochlorides **5.12a-c**

Commercially available α-amino acid methyl ester hydrochlorides **5.12a-c** were protected as their stabase adducts **5.14a-c** according to a literature method [81TL1787]. The *N*-protected α-amino esters **5.14a-c** reacted with lithium derivatives **5.2** to give ketones **5.15a-e** which were reduced with $NaBH_4$ without purification, in one pot reaction to form intermediates **5.16a-e** (Figure 5.6). After workup, diastereomeric compounds **5.16a-e** were treated with low valent titanium followed by deprotection to afford allylamines **5.18a-e** with *trans*-isomer predomination, in 40-54% overall yields based on benzotriazole derivatives **5.1** (Table 5.2).

The stabase protection was originally meant to prevent proton exchange in preparing **5.15a-e**. However, it may have also played a role in the low valent titanium effected olefination step (see the discussions below).



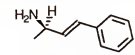
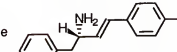
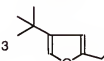
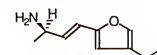
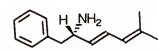
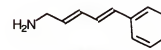
For designation of each compounds, see Table 5.2.

Figure 5.6

L-Proline Methyl Ester Hydrochloride **5.19**

The secondary amino group in compound **5.19** (Figure 5.7) was protected with triethylsilyl chloride to give ester **5.20**, which, according to integration ratios of the ^1H NMR spectrum of the crude mixture, underwent the desired reaction with lithiated 1-benzylbenzotriazole **5.2a** and subsequent reduction of ketones **5.21** and **5.22** to give a mixture of **5.23** and **5.24**. Surprisingly, the treatment of the mixture **5.23** and **5.24** with low-valent titanium under the same reaction conditions as above resulted in only 25% conversion to the product **5.25** (based on the ^1H NMR of the reaction mixture) after reflux in DME for 6 hours and prolonged heating did not help to change the conversion. The explanation is that most of the proline rings were deprotected after reduction and only **5.24** underwent the olefination under the normal conditions (Figure 5.7). The difficulty for **5.23** to proceed under the normal conditions is probably similar to a reported failure to couple

Table 5.2 Olefination of Primary α-Amino Acid Esters **5.12**

entry	Bt-deriv. **5.1**	ester **5.12**	allylamine **5.18** yield(%)/selectivity (*cis:trans*)[a]
1	 **5.1a**	D-alanine **5.12a**	 **5.18a**, 41/(1:13.1)
2	 **5.1c**	L-phenylalanine **5.12b**	 **5.18b**, 40/(1:11.0)
3	 **5.1f**	D-alanine **5.12a**	 **5.18c**, 54/(1:3.8)
4	 **5.1e**	L-phenylalanine **5.12b**	 **5.18d**, 45/(1:5.6)
5	 **5.1g**	glycine **5.12c**	 **5.18e**, 46/(1:6.8)

[a] overall yield based on **5.1**.

2-pyridyl ketones [79JOC502] under low valent titanium conditions because of the formation of a stable five-membered ring complex (Figure 5.8). Although the literature proposed Ti (III) as the coordinating metal, Zn(II) and even Cu(II) are also possible in this case. The conversion of the *N*-protected **5.16a-e** (Figure 5.6) and **5.24** (Figure 5.7) is probably due to the bulky protection groups which make the five membered-ring complex unfavorable.

It was found, however, in the presence of triethylamine dehydroxybenzotriazolylation proceeded smoothly to give the product **5.25** in 51% isolated yield (Figure 5.7). It is believed that triethylamine decomposed the five-membered ring complex by replacing the proline ring to coordinate to the metal.

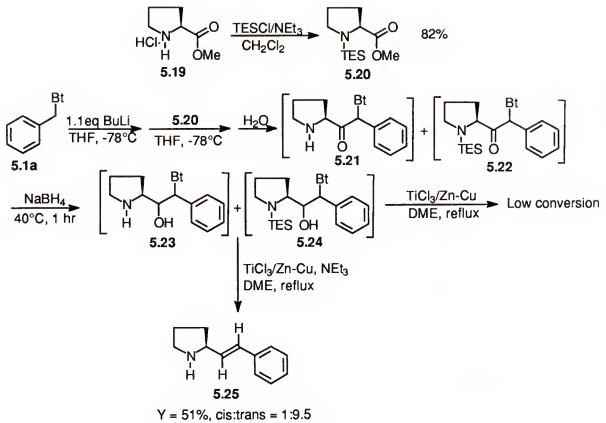


Figure 5.7

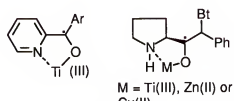


Figure 5.8

Determination of Enantiomeric Excess

Two experiments were conducted to determine the preservation of asymmetry of this procedure. The *trans*-isomer of allylamine **5.18d** (pure according to ^{1}H and ^{13}C NMR analysis) was converted into the corresponding amide **5.27** with the enantiomerically pure (S)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid **5.26** (Figure 5.9). Only a single

diastereomer **5.27** was observed in the ^{1}H NMR spectrum of the crude product and ^{13}C NMR spectrum of the purified product. Secondly, the *trans*-isomer of **5.18a** (Table 5.2), containing less than 2% of the *cis*-isomer according to ^{13}H NMR ratio, had an optical rotation of $[\alpha]^{22}_{D} = +25.8°$ (c 1.16, $CHCl_3$) in agreement with the literature value +25.9° (c = 0.9, $CHCl_3$) for 97% (R) [93HCA402]. Therefore, it can be concluded that the transformations of α-amino acid esters **5.12a-b** and **5.19** to chiral allylamines **5.18a-d** and **5.25** proceeded with at least 95% retention of the configuration at the chiral centers.

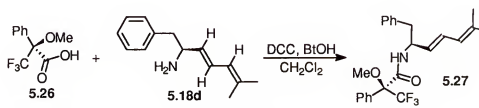


Figure 5.9

5.4 Experimental

General

THF and DME were distilled prior to use from a purple solution resulting from benzophenone and sodium. Methylene chloride for *N*- protection was distilled after reflux 24 h in the presence of P_2O_5 and was stored over molecular sieves. Zn-Cu couple was prepared and stored according to the literature method [78JOC3255]. HCl/ethanol solution was prepared by passing HCl gas through absolute alcohol and concentration calculated according to the weight difference. Column chromatography was carried out on MCB silica gel (230-400 mesh). Other chemicals were used as obtained from commercial sources. The

(S)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid **5.26** was over 98.5% enantiomerically pure according to the commercial source.

Reactions were routinely carried out under dry nitrogen or argon atmosphere with magnetic stirring.

Melting points were determined on a hot stage apparatus without correction. NMR spectra were obtained with a Varian Gemini-300 spectrometer at 75 MHz for ^{13}C and 300 MHz for ^{1}H. Both ^{13}C and ^{1}H NMR spectra were obtained in chloroform-*d*, chemical shift values are reported as δ downfield from TMS as an internal standard. The NMR spectra reported were for *trans*-isomers unless otherwise stated. High-resolution mass spectra and elemental analyses were performed within the department. Optical rotation values reported for **5.18b-d** and **25** were of the mixtures of *cis*- and *trans*-isomers and for **5.18a** of the purified *trans*-isomer, and were measured with a Perkin-Elmer 341 polarimeter with the use of sodium D line.

Preparation of 2-(Benzotriazol-1-yl)methyl-4-(*t*-butyl)furan (**5.1f**) (By Mrs. C. Fali)

A solution of *n*-BuLi (37.5 mL of 1.6 M in hexane, 60 mmol) was added dropwise with stirring to a solution of 1-propargylbenzotriazole [95JOC638] (9.6 g, 60 mmol) in THF (100 mL) at -78 °C. The mixture was stirred at this temperature for 1 h, and bromomethyl *t*-butyl ketone (10.74 g, 60 mmol) was added slowly. The mixture was stirred for 4 h and *t*-BuOK (6.7 g, 60 mmol) in *t*-BuOH (30 mL) was added. The reaction was warmed to room temperature, and heated at 50 °C overnight. Water (100 mL) and EtOAc (100 mL) were added and the organic phase washed with ammonium chloride (3 x 100 mL) and dried with $MgSO_4$. After removal of the solvents, the residue was subjected to silica gel column chromatography using ether/hexane (1:3) as eluent to give **5.1f** as white powder (11.48 g, 75%): mp 63-5 °C; ^{1}H NMR δ 1.54 (s, 9 H), 5.77 (s, 2 H), 6.39 (s, 1 H), 7.12 (s, 1 H), 7.37 (t, *J* = 7.7 Hz, 1 H), 7.48 (t, *J* = 7.7 Hz, 1 H), 7.59 (d, *J* =8.4 Hz, 1 H), 8.06 (d,

J = 8.1 Hz, 1 H); ^{13}C NMR δ 45.2, 30.6, 29.8, 147.8, 146.1, 137.3, 137.2, 132.8, 127.4, 123.8, 119.8, 109.8, 109.2. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.62; H, 7.07; N, 16.58.

General procedure for preparation of α-benzotriazol-1-yl ketones **5.8a-h**

To a THF (40 mL) solution of **5.1a-d** (8 mmol) in a lithiation bottle at -78 °C and protected with nitrogen or argon, the base (Table 1) was added dropwise and a dark blue solution was obtained and was stirred at -78 °C for 15 min. The corresponding ester **5.6a-g** (8.4 mmol) was added dropwise in dry THF (5 mL) and the temperature raised if necessary (Table 5.1). After the dark color dissappeared, saturated NH_4Cl solution (20 mL) was added. After the mixture reached room temperature, it was diluted with methylene chloride (80 mL) and water (50 mL). The organic phase was separated and washed with water (80 mL) and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure followed by separation (see each compound) gave the product **5.8a-h** (see Table 5.1 for yields).

α-Phenyl-α-(benzotriazol-1-yl)methyl 4-methylphenyl ketone (**5.8a**), crystallization in ether: mp 161-3 °C; ^1H NMR δ 2.40 (s, 3 H), 7.20-7.40 (m, 10 H), 7.86 (s, 1 H), 7.91 (d, J = 8.1 Hz, 2 H), 8.00 - 8.05 (m, 1 H); ^{13}C NMR δ 21.7, 68.1, 111.6, 120.0, 123.8, 127.4, 129.1, 129.26, 129.34, 129.7, 132.1, 133.24, 133.29, 145.4, 146.7, 192.2 (one carbon unresolved). Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 76.91; H, 5.25; N, 12.95.

α-Phenyl-α-(benzotriazol-1-yl)methyl *n*-heptyl ketone (**5.8b**), Silica gel column chromatography with hexane/ethyl acetate (1:1) as eluent: mp 88-9 °C; ^1H NMR δ 0.84 (t, J = 6.5 Hz, 3 H), 1.12 - 1.32 (m, 8 H), 1.60 - 1.66 (m, 2 H), 2.61 (t, J = 7.3 Hz, 2 H), 6.78 (s, 1 H), 7.20-7.40 (m, 8 H); 8.04 (d, J = 7.8 Hz, 1 H); ^{13}C NMR δ 14.0, 22.5, 23.6, 28.8, 31.5, 40.8, 71.3, 110.7, 120.0, 123.9, 127.5, 129.0, 129.2, 129.4, 132.5, 133.0, 146.3,

203.1 (one carbon unresolved). Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.52; N, 12.53. Found: C, 75.01; H, 7.92; N, 12.60.

α-1-Naphthyl-α-(benzotriazol-1-yl)methyl *iso*-butyl ketone (**5.8c**), crystallization in hexane/ethyl acetate (1:1): mp 124-5 °C; ^{1}H NMR δ 0.97-1.01 (m, 6 H), 2.27-2.37 (m, 1 H), 2.62 (d, *J* = 6.9 Hz, 2 H), 7.10-8.12 (m, 12 H); ^{13}C NMR δ 22.4, 22.6, 24.9, 68.7, 111.1, 120.0, 122.7, 123.7, 124.8, 126.6, 127.2, 127.4, 127.5, 127.7, 129.2, 130.9, 132.1, 133.3, 134.3, 146.5, 203.4. Anal. Calcd for $C_{22}H_{21}N_3O$: C, 76.93; H, 6.17; N, 12.24. Found: C, 76.81; H, 6.20; N, 12.21.

α-1-Naphthyl-α-(benzotriazol-1-yl)methyl *t*-butyl ketone (**5.8d**), crystallization in 1:1 hexane/ethyl acetate: mp 188-9 °C; ^{1}H NMR δ 1.31 (s, 9 H), 7.16-7.28 (m, 3 H), 7.48-7.52 (m, 2 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.66 (d, *J* = 6.9 Hz, 1 H), 7.87-8.18 (m, 5 H); ^{13}C NMR δ 26.7, 44.9, 63.7, 111.9, 119.8, 122.5, 123.6, 124.6, 126.6, 127.0, 127.2, 127.5, 127.8, 129.2, 131.1, 131.7, 133.5, 134.4, 146.7, 209.7. Anal. Calcd for $C_{22}H_{21}N_3O$: C, 76.93; H, 6.17; N, 12.24. Found: C, 76.67; H, 6.32; N, 12.15.

α-(4-Methylphenyl)-α-(benzotriazol-1-yl)methyl 4-dimethylaminophenyl ketone (**5.8e**), silica gel column chromatography with ethyl acetate as eluent: mp > 200 °C; ^{1}H NMR δ 2.33 (s, 3 H), 3.06 (s, 6 H), 6.63 (d, *J* = 9.0 Hz, 2 H), 7.16, (d, *J* = 7.5 Hz, 2 H), 7.28-7.31 (m, 5 H), 7.83 (s, 1 H), 7.92 (d, *J* = 9.0 Hz, 2 H), 8.00 - 8.04 (m, 1H); ^{13}C NMR δ 21.2, 39.9, 67.5, 110.9, 112.2, 119.7, 123.6, 127.1, 128.4, 129.0, 129.8, 131.1, 131.3, 133.4, 139.0, 146.7, 153.9, 190.2. Anal. Calcd for $C_{23}H_{22}N_4O$: C, 74.56; H, 5.99; N, 15.13. Found: C, 74.38; H, 6.02; N, 15.18.

α-(4-Dimethylaminophenyl)-α-(benzotriazol-1-yl)methyl 4-methylphenyl ketone (**5.8f**), crystallization in hexane/ethyl acetate (1:1): mp 164-5 °C; ^{1}H NMR δ 2.41 (s, 3 H), 2.96 (s, 6 H), 6.67 (d, *J* = 9.0 Hz, 2 H), 7.21-7.32 (m, 7 H), 7.80 (s, 1 H), 7.93 (d, *J* = 8.1 Hz, 2 H), 8.02-8.05 (m, 1 H); ^{13}C NMR δ 21.7, 40.0, 68.5, 112.0, 112.4, 119.6, 119.8,

123.5, 127.1, 129.1, 129.6, 130.3, 132.3, 133.5, 144.9, 146.7, 150.8, 192.9. Anal. Calcd for $C_{23}H_{22}N_4O$: C, 74.56; H, 5.99; N, 15.13. Found: C, 74.47; H, 6.18; N, 15.02.

α-(4-Methylphenyl)-α-(benzotriazol-1-yl)methyl 2-thiophenyl ketone (**5.8g**), crystallization in hexane/ethyl acetate (1:1): mp 104-7 °C; ^{1}H NMR δ 2.34 (s, 3 H), 7.11 (t, J = 4.5 Hz, 1 H), 7.20 (d, J = 7.8 Hz, 2 H), 7.28-7.40 (m, 5 H), 7.67 (s, 1 H), 7.70-7.68 (m, 2 H), 8.00-8.08 (m, 1 H); ^{13}C NMR δ 21.2, 68.6, 111.6, 120.0, 123.9, 127.5, 128.6, 128.9, 130.0, 133.1, 133.9, 135.5, 139.6, 141.4, 146.7, 185.7 (one carbon unresolved). Anal. Calcd for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.54; N, 12.61. Found: C, 68.22; H, 4.38; N, 12.58.

α-(4-Methylphenyl)-α-(benzotriazol-1-yl)methyl 2-(N-methylpiperidinyl) ketone (**5.8h**) (a mixture of two diastereomers), silica gel column chromatography with methylene chloride/methanol (100:5) as eluent: mp 151-2 °C; ^{1}H NMR δ 1.21-1.99 (m, 6 H), 2.01-2.42 (m, 7 H), 2.91-3.94 (m, 2 H), 7.02-8.06 (m, 9 H). Anal. Calcd for $C_{21}H_{24}N_4O$: C, 72.37; H, 6.95; N, 16.09. Found: C, 72.31; H, 7.09; N, 16.05.

General Procedure for Generating the Low Valent Titanium

To a 250 mL three-neck flask under argon protection, Zn-Cu (5.4 g) was added and the system was degased and protected with argon. $TiCl_3$ (3.85 g 15 mmol) was quickly weighed and added to the flask which was again degased and protected with argon. Under stirring, dry DME (40 mL) was added with syringe and the mixture was refluxed for 5 h and cooled to room temperature. (With $TiCl_3$/Li, see literature [97JOC238]).

General Procedure for Preparation of **5.10a-g**

α-Benzotriazol-1-yl ketone **5.8a-h** (5 mmol) was heated to reflux for 15 min with $NaBH_4$ (0.5 g) in ethanol (40 mL, 200 proof) and cooled down to room temperature. The reaction mixture was then slowly poured into saturated NH_4Cl solution (50 mL). Methylene

chloride (100 mL) was added and the mixture stirred vigorously for 5 min. After the organic phase was separated, it was washed with 5% NaCl solution (50 mL) and water (50 mL) and dried with $MgSO_4$. Hexane (20 mL) was added and the solution was concentrated under reduced pressure to give the corresponding intermediate **5.9a-h** as a mixture of diastereomers. Mixture **5.9a-h** was added with DME (20 mL) to the low valent titanium mixture (generated as described above) and the mixture was refluxed overnight. Then it was cooled down, filtered and the solid residue extracted with methylene chloride (2 x 100 mL). The combined organic phase was washed with saturated NH_4Cl (100 mL), 10% Na_2CO_3 (100 mL) and water (100 mL). and dried with $MgSO_4$. Evaporation of the solvent followed by column chromatography (for eluents, see each compound below) gave **5.10a-g** (see Table 5.1 for yields).

trans-1-Phenyl-2-[*p*-toluyl]ethylene (**5.10a**): hexanes as eluent; mp 119-120 °C (lit [87S284] mp 119-120 °C); ^{1}H NMR δ 2.35 (s, 3 H), 7.07 (s, 2 H), 7.16 (d, *J* = 8.1 Hz, 2 H), 7.22-7.27 (m, 1 H), 7.34 (t, *J* = 7.7 Hz, 2 H), 7.41 (d, *J* = 8.1 Hz, 2 H), 7.49 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR δ 21.2, 126.4, 127.4, 127.8, 128.3, 128.4, 128.6, 129.4, 134.61, 137.5, 137.6.

trans-1-Phenyl-1-nonene (**5.10b**) [73CB1612]: hexanes as eluent; oil; ^{1}H NMR δ 0.89 (t, *J* = 6.5 Hz, 3 H), 1.15-1.55 (m, 10 H), 2.20 (q, *J* = 7.0 Hz, 2 H), 6.22 (dt, *J* = 6.6 Hz, 15.9 Hz, 1 H), 6.38 (d, *J* = 15.9 Hz, 1 H), 7.14-7.35 (m, 5 H); ^{13}C NMR δ 14.1; 22.7; 29.2, 29.4; 31.9; 33.1; 125.9; 126.7; 128.4; 129.7; 131.2; 138.0 (one carbon unresolved).

trans-1-(1-Naphthyl)-4-methyl-1-pentene (**5.10c**): hexanes as eluent; oil; ^{1}H NMR δ 0.99 (d, *J* = 6.6 Hz, 6 H), 1.70-1.90 (m, 1 H), 2.15-2.25 (t, *J* = 7.2 Hz,2 H), 6.21 (dt, *J* = 15.4 Hz, 7.4 Hz, 1 H), 7.08 (d, *J* = 15.6 Hz, 1 H), 7.35-7.60 (m, 4 H), 7.70-7.80 (m, 1 H), 7.80-7.90 (m, 1 H), 8.10-8.20 (m,1 H); ^{13}C NMR δ 22.4, 28.6, 42.8, 123.6, 124.0, 125.6, 125.7, 125.8, 127.2, 128.1, 128.4, 131.2, 133.2, 133.6, 135.9. Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C 91.60, H, 9.01.

trans-1-(1-Naphthyl)-3,3-dimethyl-1-butene (**5.10d**): hexanes as eluent; oil; ^{1}H NMR δ 1.21 (s, 9 H), 6.26 (d, *J* = 15.9 Hz, 1 H), 7.04 (d, *J* = 15.9 Hz, 1 H), 7.25-7.56 (m, 4 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 7.81-7.85 (m, 1 H), 8.10-8.15 (m, 1 H); ^{13}C NMR δ 29.7, 33.8, 121.9, 123.5, 124.0, 125.6, 125.7, 125.7, 127.1, 128.5, 131.4, 133.7, 136.0, 145.3. Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.61; H, 9.03.

trans-(*p*-Methyl)-*p*'-(dimethyl)aminostilbene (**5.10e**): methylene/hexane (1:1) as eluent; mp 163-5 °C; ^{1}H NMR δ 2.34 (s, 3 H), 2.97 (s, 6 H), 6.71 (d, *J* = 9.0 Hz, 2 H), 6.88 (d, *J* = 16.2 Hz, 1 H), 7.00 (d, *J* = 16.2 Hz, 1 H), 7.13 (d, *J* = 8.1 Hz, 2 H), 7.30-7.42 (m, 4 H); ^{13}C NMR δ 21.2, 40.5, 112.5, 124.4, 125.9, 126.0, 127.4, 127.8, 129.3, 135.4, 136.4, 150.0. Anal. Calcd for $C_{17}H_{19}N$: C, 86.02, H, 8.07, N, 5.90. Found: C, 86.11; H, 8.45, N, 6.10.

trans-1-(4-Methylphenyl)-2-thiophenylethylene (**5.10f**): hexanes as eluent; mp 104-7 °C (lit. mp 115-6°C [73JHC643]); ^{1}H NMR δ 2.36 (s, 3 H), 6.91 (d, *J* = 16.2 Hz, 1 H), 6.97-7.30 (m, 6 H), 7.37 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR δ 21.2, 120.9, 124.0, 125.7, 126.2, 127.5, 128.4, 129.4, 134.2, 137.5, 143.2. Anal. Calcd for $C_{13}H_{12}S$: C, 77.97, H, 6.04. Found: C, 77.71; H, 6.19.

1-*p*-Toluyl-2-[2-(*N*-methylpiperidinyl)]ethylene (**5.10g**): alumina oxide (activated, neutral, 50-200 micron) with hexane/ethyl acetate (1:1) as eluent; oil; ^{1}H NMR (*cis*- and *trans*-isomers) δ 1.2-1.8 (m, 6 H, *cis* and *trans*), 1.9-2.1 (m, 1 H, *cis* and *trans*), 2.20 (s, 3 H, *cis*), 2.24 (s, 3 H, *trans*), 2.33 (s, 3 H, *trans*), 2.35 (s, 3 H, *cis*), 2.40-2.50 (m, 1 H, *cis* and *trans*), 2.80-3.00 (m, 1 H, *cis* and *trans*), 5.6 (dd, *J* = 12 Hz, 9.8 Hz, 1 H, *cis*), 6.1 (dd, *J* = 15.9 Hz, 8 7 Hz, 1 H, *trans*), 6.40-6.50 (m, 1 H, *cis* and *trans*), 7.0-7.3 (m, 4 H, *cis* and *trans*); ^{13}C NMR δ (*cis*- and *trans*-isomers) 21.1, 23.8, 24.0, 26.0, 29.7, 32.5, 33.5, 44.3, 44.6, 44.7, 56.3, 56.5, 61.8, 68.1, 126.1, 128.6, 128.8, 129.2, 129.4, 130.4, 132.7, 134.4, 134.6, 135.6, 136.3, 137.0. Anal. Calcd for $C_{15}H_{21}N$: N, 6.51; Found: N, 6.72.

Procedure for Preparation of *trans*-1-[3-(2-methylfuranyl)]-4-methyl-1,3-pentadiene (**5.10h**)

1-(Benzotriazol-1-yl)-3-methyl-2-butene **5.1e** (0.90 g, 4.8 mmol) was dissolved in dry THF (30 mL) in a lithiation bottle protected under argon or nitrogen and the mixture cooled down to -78 °C. *n*-BuLi hexane solution (3.3 mL of 1.6 M) was added. After 15 min, methyl 2-methyl-3-furancarboxylate (**5.6h**) (0.74g, 5.3 mmol) in dry THF (4 ml) was added dropwise. After the color released (within about 5 minutes), the reaction was quenched with water (30 mL) followed by addition of $NaBH_4$ (0.8 g, 21.0 mmol). The mixture was warmed and maintained at 40 °C for 1 h. Ether (100 mL) was added and the organic phase separated and dried with $MgSO_4$. After evaporation of the solvents, the residue was dried *in vacuo*, protected under argon, and transferred *via* syringe using dry DME (2 x 15 mL) to the low-valent titanium mixture. The reaction mixture was refluxed for 2 h and was cooled to room temperature, filtered and the solid residue extracted with ether (2 x 100 mL). The combined organic phase was washed with saturated $NaHCO_3$ (2 x 100 mL), brine (100 mL) and water (100 mL) and dried with $MgSO_4$. Evaporation of the solvent followed by silica gel column chromatography with hexane/ethyl acetate (1:1) as the eluent gave the product **5.10h** as an oil (0.46 g, 59%): ^{1}H NMR δ 1.84 (s, 6 H), 2.31 (s,3 H), 5.96 (d, *J* = 10.8 Hz, 1 H), 6.24 (d, *J* = 15.3 Hz, 1 H), 6.50 (d, *J* = 1.5 Hz, 1 H), 6.60 (dd, *J* = 10.8 Hz, 15.3 Hz, 1 H), 7.24 (d, *J* = 1.8 Hz, 1 H); ^{13}C NMR δ 11.7, 18.4, 26.1, 107.8, 119.2, 119.7, 124.3, 125.5, 134.4, 140.7, 148.9. Anal. Calcd for $C_{11}H_{14}O$: C, 81.43; H, 8.70; O, 9.87. Found: C, 81.66; H, 9.10.

General Procedure for Preparation of *N*-Protected α-Amino Acid Esters **5.14a-c**

To α-amino acid methyl ester hydrochloride **5.12a-c** (20 mmol) in a three-neck round bottom flask under argon was added triethylamine (61 mmol) with dry methylene chloride (15 mL) and the mixture cooled to 0 °C. 1,2-Bis(chlorodimethylsilyl)ethane (**5.13**)

(4.73 g, 22 mmol, 96%) was added dropwise with dry CH_2Cl_2 (15 mL). The mixture was stirred at 40 °C for 1 h, diluted with hexane, and filtered. The filtrate was evaporated and dried *in vacuo*. Hexane was added to the residue followed by filtration with fine sintered glass filter to get a clear solution which was then concentrated under reduced pressure to give a clear oil **5.14a-c**.

General Procedure for Preparation of Primary Allylamines **5.18a-e**

Compound **5.1a,c,e,f,g** (6.4 mmol) was dissolved in dry THF (30 mL) in a lithiation bottle protected under argon or nitrogen and the mixture cooled down to -78 °C. *n*-BuLi hexane solution (4.4 ml of 1.6 M) was added. After 15 min, the corresponding *N*-protected ester **5.14a-c** (7.0 mmol) (prepared as described above) in dry THF (4 mL) was added dropwise (and then the temperature raised to about 0 °C for entry 5, Table 5.2). After the dark color dissappeared, the reaction mixture was quenched with water (30 mL) followed by addition of $NaBH_4$ (0.9 g, 23.7 mmol). The mixture was warmed and maintained at 40 ° C for 1 h. Ether (100 mL) was added and the organic phase separated and dried with K_2CO_3. After evaporation of the solvents, the residue was dried *in vacuo*, protected under argon, and transferred with dry DME (2 x 15 mL) to the low valent titanium mixture. The reaction mixture was refluxed for 2 h and decanted to a sintered glass filter. Both the filtrate and the solid residue were quenched with 15% KOH solution (100 mL) and extracted* with solvents (100 mL, 2 x 50 mL, 1:1 ethyl acetate and ether for the DME filtrate; ether for the solid residue) The organic phases were combined, dried with K_2CO_3 and subjected to evaporation. The residue was diluted with ether (20 mL) and treated with 1M HCl ethanol solution (20 mL). After stirred for 1 h, the mixture was basified with saturated K_2CO_3 solution (50 mL). CH_2Cl_2 (100 mL) was added and the organic phase separated and dried with K_2CO_3. Column chromatography of the residue (first 100:5 methylene chloride and methanol to elute other fractions and then 100:5:1 methylene chloride, methanol and

triethylamine to fully rinse out the products) gave products **5.18a-e**. (* Moderate stirring for 10 to 15 min is recommended instead of vigorous shaking to get good separation. In case phase separation is hard to complete, filtration can be used to solve the problem.)

D-*trans*-1-Phenyl-3-amino-1-butene (**5.18a**): oil; $[\alpha]^{22}_D$ +25.8° (c 1.16, $CHCl_3$), lit. value +25.9° (c 0.9, $CHCl_3$) [93HCA402]; ^1H NMR δ 1.22 (d, *J*= 6.3 Hz, 3 H), 1.92 (br s, 2 H), 3.60-3.66 (m, 1 H), 6.17 (dd, *J* = 6.6 Hz, 15.9 Hz, 1 H), 6.43 (d, *J* = 15.9 Hz, 1 H), 7.10-7.40 (m, 5 H). ^{13}C NMR δ 23.7, 49.3, 126.2, 127.2, 128.0, 128.5, 135.7, 137.0.

L-*trans*-1-*p*-(Toluyl)-3-amino-4-phenyl-1-butene (**5.18b**): oil; $[\alpha]^{22}_D$ +37.9° (c 1.01, $CHCl_3$); ^1H NMR δ 1.40 (br s, 2 H), 2.32 (s, 3 H), 2.68 (dd, J = 8.1Hz, 13.5Hz, 1 H), 2.90 (dd, *J* = 5.1 Hz, 13.5 Hz, 1 H), 3.72-3.76 (m, 1 H), 6.21 (dd, *J* = 6.9 Hz, 15.9 Hz, 1 H), 6.46 (d, *J* = 15.6 Hz, 1 H), 7.00-7.40 (m, 9 H); ^{13}C NMR δ 21.1, 44.6, 55.1, 126.1, 126.3, 128.3, 128.8,129.2, 129.4, 132.9, 134.2, 137.0, 138.6. HRMS calcd for $C_{17}H_{19}N$ m/e 237.1517, found m/e 237.1496.

D-*trans*-1-[4-(*t*-Butyl)]furan-2-yl-3-amino-1-butene (**5.18c**): oil; $[\alpha]^{22}_D$ +3.2° (c 1.21, $CHCl_3$); ^1H NMR δ 1.16-1.23 (m, 12 H), 1.69 (br s, 2 H), 3.55-3.65 (m,1 H), 6.11 (dd, *J* = 6.3 Hz, 15.9 Hz, 1 H), 6.17 (s, 1 H), 6.24 (d, *J* = 15.9 Hz, 1 H), 7.07 (s, 1 H); ^{13}C NMR δ 23.8, 30.7, 45.2, 48.9, 106.9, 116.6, 134.6, 135.9, 137.8, 152.6. Anal. Calcd for $C_{12}H_{19}NO$: N, 7.25. Found: N, 7.64.

L-*trans*-2-Methyl-6-amino-7-phenyl-2,4-heptadiene (**5.18d**): oil; $[\alpha]^{22}_D$ +36.6° (c 0.99, $CHCl_3$); ^1H NMR δ 1.20 (br s, 2 H), 1.75 (s, 3 H), 1.78 (s, 3 H), 2.61 (dd, *J* = 8.3 Hz, 13.4 Hz, 1 H), 2.87 (dd, *J* = 5.1 Hz, 13.2 Hz, 1 H), 3.60-3.70 (m, 1 H), 5.60 (dd, *J* = 6.9 Hz, 15.0 Hz, 1 H), 5.82 (d, *J* = 10.5 Hz, 1 H), 6.37 (dd, J = 10.8 Hz, 15.0 Hz, 1 H), 7.20-7.40 (m, 5 H); ^{13}C NMR δ 18.2, 25.9, 44.8, 54.9, 124.5, 125.7, 126.2, 128.3, 129.3, 134.8, 138.9 (one carbon unresolved). HRMS calcd for $C_{14}H_{19}N$ m/e 201.1517, found m/e 201.1543.

trans, trans-1-Phenyl-5-amino-1,3-pentadiene (**5.18e**): oil: ^1H NMR δ 1.53 (br s, 2 H), 3.41 (d, *J* = 5.7 Hz, 2 H), 5.92 (dt, *J* = 15.3 Hz, 6.0 Hz, 1 H), 6.32 (dd, *J* = 10.5 Hz,

15.3 Hz, 1 H), 6.50 (d, *J* = 15.6 Hz, 1 H), 6.79 (dd, *J* = 10.5 Hz, 15.6 Hz, 1 H), 7.15-7.45 (m, 5 H); ^{13}C NMR δ 44.0, 126.2, 127.3, 128.5, 128.6, 130.0, 131.5, 135.5, 137.3. Anal. Calcd for $C_{11}H_{13}N$: N, 8.80. Found: N, 8.53.

Preparation of L-*trans*-1-(2-Pyrrolidinyl)-2-phenylethylene (**5.25**)

Ester **5.20** was prepared in a similar way to **14a-c** except that only 2.05 eq of triethylamine was used. The procedure of preparation of **5.25** is similar to that of **5.18a-e** except that triethylamine (2 mL, corresponding to 6.4 mmol of **5.1a**) was present in the low valent titanium mixture and there was no HCl/ethanol treatment: oil; $[\alpha]^{22}_{D}$ -64.5° (c 1.28, $CHCl_3$); ^{1}H NMR δ 1.50-1.70 (m, 1 H), 1.71-1.95 (m, 2 H), 1.96-2.15 (m, 1 H), 2.40-2.6 (br s, 1 H), 2.85-3.05 (m, 1 H), 3.05-3.20 (m, 1 H), 3.60-3.80 (m, 1 H), 6.23 (dd, *J*= 7.2 Hz; 15.9 Hz; 1 H), 6.53 (d, *J* = 15.9 Hz, 1 H), 7.10-7.50 (m, 5 H); ^{13}C NMR δ 25.2, 32.3, 46.4, 60.9, 126.2, 127.2, 128.4, 129.7, 132.4, 137.1. HRMS calcd for $C_{12}H_{15}N$ m/e 173.1205, found m/e 173.1206.

Preparation of N-6-(S-trans-2-Methyl-7-phenyl-2,4-heptadienyl)-S-(-)-α-methoxy-α-(tryfluoromethyl)phenylacetamide (**5.27**)

Amine **5.18d** (100 mg, 0.5 mmol) was mixed with 1.2eq of the acid **5.26** (Figure 5.9), 1.2 eq of 1-hydroxybenzotriazole, and 2 eq of DCC (1,3-dicyclohexylcarbodiimide) in dry CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 1 h. Filtration, evaporation, and silica gel column chromatography (methylene chloride/hexane) gave product **5.27** as an oil (only one diastereomer found, 0.21 g, 88%): ^{1}H NMR δ 1.63 (s, 3 H), 1.77 (s, 3 H), 2.84 (dd, *J* = 7.5 Hz, 13.8 Hz, 1 H), 3.00 (dd, *J* = 6.6 Hz, 13.8 Hz, 1 H), 3.22 (s, 3 H), 4.92 (m, 1 H), 5.49 (dd, *J* = 6.3 Hz, 15.3 Hz, 1 H); 5.77 (d, *J* = 10.8 Hz, 1 H); 6.24 (dd, *J* = 11.1 Hz, 15.0 Hz, 1 H), 6.64 (d, *J* = 8.7 Hz, 1 H), 7.20-7.60 (m, 10 H);

^{13}C NMR 18.4, 25.9, 41.3, 51.7, 54.8, 83.9 (q, J = 26 Hz, C-CF_3), 124.0; 123.6 (q, J = 288 Hz, CF_3), 126.6, 127.4, 127.7, 128.4, 128.7, 129.3, 132.9, 136.2, 137.0, 165.3.

CHAPTER 6
CONCLUSION

By utilizing the versatile properties of 1-benzotriazolyl group, benzotriazole-mediated synthesis has been applied in several different areas of organic transformation.

(*N,N*-dialkylaminoalkyl)benzotriazoles was used as a generalized iminium ion equivalent in the thiazolium salt catalyzed synthesis of α-amino ketones from aldehydes. Although cross-over and β-H elimination limit the generality of this method, it can be used to synthesize some α-substituted α-amino ketones which can not be synthesized by the literature method.

N,N-Dimethylbenzotriazolylmethyleneiminium chloride was found to resemble Vilsmeier reagents in reactions with nucleophiles. Under basic conditions it can react with phenyl isocyanate followed by different work-up reagents to give hydantoins with various functionalities at 5-position in one-pot processes which provide a useful approach to this system.

Because of their higher reactivity, BetMIC derivatives have been shown to give better results than TosMIC in synthesizing some pyrroles and imidazoles, especially in reacting with less reactive electrophiles.

A new method of diastereoselective olefination of carboxylic esters has been established featuring low valent titanium effected dehydroxybenzotriazolylation. This method was elaborated successfully to transform α-amino acid esters into allylamines with both diastereoselectivity for *trans*-isomers and virtually full retention of the asymmetry, providing a novel, cheap and simple route to this type of biologically important compounds.

Thus, benzotriazole-mediated synthesis proved to be useful in improving a variety of organic transformations and in achieving new organic transformations.

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The reference citation system employed throughout this dissertation is that from "Comprehensive Heterocyclic Chemistry" (Vol. 1) Pergamon Press, 1984 (eds. Katritzky, A. R. and Rees, C. W.).

Each time a references is cited, a number and letter code appear in a bracket, for example [00ABC000]. The first two digits denote the year of the twentieth century, the letter code is an abbreviation for the journal or book cited and the digits after the letter code represent the page number in the journal or the book. Additional notes to this reference system are as follows:

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iv). Books and journals which are less commonly used are called "MI" for miscellaneous.

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BIOGRAPHICAL SKETCH

Dai Cheng was born on July 22nd, 1962, in Baise, Guangxi, P. R. China. In 1984, he finished his undergraduate study in the major of Physical Chemistry and Instrumental Analysis and received a B. S. degree from Department of Chemistry and Chemical Engineering, Tsinghua University. He shifted his research interest to organic synthesis by joining Professor Z. Liu's group, Department of Chemistry, Tsinghua University, and received a master's degree in applied chemistry in 1987. He worked as a teaching and research associate in Department of Chemistry, Guangxi University, from 1987 to 1989. Then he suspended his work in Guangxi University and started working as a research associate/service engineer for Houghton(China), Shenzhen. In fall 1993, he entered the Department of Chemistry, University of Florida, as a graduate student and joined Professor A. R. Katritzky's group where he worked on benzotriazole-mediated synthetic methodology and some joint projects with industry.

Besides chemistry, he enjoys music, swimming, playing table-tennis and go (weiqi).

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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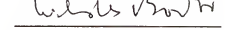

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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